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FAILURE OF ADRENOCORTICOTROPHIC HORMONE OR CORTISONE TO INFLUENCE EPINEPHRINE-INDUCED FEVER IN THE RABBIT*

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Received for publication February 11, 1955

The febrile response of human beings and of rabbits after injection of bacterial pyrogen can be altered by prior treatment with adrenocorticotrophic hormone (ACTH) or cortisone (1–4). This change takes the form of attenuation of fever in human subjects with the doses of these hormones ordinarily employed, but in rabbits, depending upon dosage and time of administration of hormone and dosage of pyrogen, there may be suppression, aggravation, or no modification of the febrile response (3, 4). The mechanism of these effects of adrenal steroids upon temperature regulation is unknown.

Fever in rabbits after injection of bacterial pyrogens is predominantly a result of decreased heat loss due to peripheral vasoconstriction (5) and there is much evidence to indicate that pyrogen fever is mediated by some adrenalin-like substance. Pinkston found lowered fevers after typhoid vaccine injection in sympathectomized cats (6) and it was shown by Feldman and Gellhorn (7) that removal of the adrenal medulla in rats results in a fall in temperature after pyrogen administration although normal or vagotomized rats respond to pyrogens with hyperthermia. Wells and Rall found no significant difference in the febrile response of normal and curarized dogs to pyrogen (8) but employing an adrenergic blocking drug, they obtained delayed onset and reduced magnitude of fevers in both normal and curarized animals (9). Boquet and his collaborators showed that the initial event after injection of typhoid pyrogen in rabbits is severe peripheral vasoconstriction (10, 11) and that denervation of the ear results in an intensification of the vasoconstrictor response to pyrogen in this area in much the same manner that denervation renders peripheral vessels more sensitive to epinephrine (12). Furthermore, prior administration of Dibenamin, an adrenolytic drug, inhibits the peripheral vasoconstriction produced by pyrogen in rabbits (13). It may also be mentioned that nearly 30 years ago von Euler (14) demonstrated the presence of a substance with many of the properties of epinephrine in the blood of patients with febrile diseases. The evidence relating the action of bacterial pyrogens to epinephrine or similar substances has recently been reviewed in detail by Thomas (15).

Because of the importance of peripheral vasoconstriction in the response of

*This study was supported by Grant A-660 of the National Institute of Arthritis and Metabolic Diseases, U. S. Public Health Service.

the rabbit to injection of bacterial pyrogen, it was thought that the influence of ACTH and cortisone upon fever in this animal might be the result of altered reactivity of the peripheral vasculature. This possibility has been tested experimentally by observing the effects of administration of these hormones upon the febrile response of rabbits after injection of epinephrine and norepinephrine. The results of these experiments form the basis of the present report. A few observations upon pyrogen tolerance and Thorotrast in relation to epinephrine are also included.

MATERIALS AND METHODS

Male rabbits of mixed breed weighing 2 to 3 kilos were used.

Bacterial pyrogens employed were typhoid vaccine containing one billion organism /...l. (obtained from the Georgia State Department of Health) and Piromen, a *Pseudomonas* concentrate, (kindly supplied by Baxter Laboratories as a suspension containing 50 mcgm./ml.).

ACTH was purchased commercially as a solution containing 40 U.S.P. units/ml. (Wilson). Cortisone acetate was kindly supplied by Merck and Company as a suspension containing 25 mg./ml. Epinephrine was used as a solution containing 1.82 mgm./ml. of epinephrine bitartrate (Winthrop-Stearns), equivalent to 1.0 mgm./ml. of the base. *l*-norepinephrine was used as a solution containing 2.0 mgm./ml. of the bitartrate salt (Winthrop-Stearns), equivalent to 1.0 mgm./ml. of the base.

To measure febrile responses, animals secured by a loose-fitting collar, were placed in metal stalls and rectal temperatures were taken at intervals of 30 minutes using resistance coils which remained in the rectum throughout the test period and by an automatic recording device (the Foxboro Rabbit Scanner and Fever Recorder). In a few experiments, rectal and skin temperatures were recorded at shorter intervals using a six-channel Telethermometer (Yellow Springs Instrument Co.) with resistance coils. Before use rabbits were allowed appropriate periods of acclimatization in the stalls and an adequate number of baseline recordings was made before each experimental procedure. To facilitate comparison of results, fever curves of individual animals were charted on standard graph paper and the areas under the curves were measured with a planimeter (Keuffel and Esser #4236M). The vernier reading of this instrument was taken as the "fever index", an indication of both height and duration of fever (16).

All glassware, needles, etc. were sterilized in hot-air ovens at 170°C. to destroy pyrogen contaminants. Saline solutions were tested at regular intervals by intravenous injection into normal rabbits and were always pyrogen-free.

EXPERIMENTAL RESULTS

Febrile Response of Normal Rabbits to Epinephrine and l-*Norepinephrine*

Several dosages of epinephrine were employed in preliminary experiments attempting to produce consistent febrile responses in normal rabbits. Although the *intravenous* administration of doses as large as 1.0 mgm. resulted in intense vasoconstriction, this effect was transient. Several animals died within 30 minutes and rises in rectal temperature were not regularly observed. Furthermore, the temperature responses of surviving animals to repeated intravenous injections were unpredictable from day to day. As a consequence, comparison of results in the same animal or different animals was not feasible.

In experiments employing epinephrine by the *intramuscular* route, it was found that repeated injections of small quantities resulted in sustained vasoconstriction and rise in rectal temperature. The technique finally employed consisted of a series of five injections of 0.2 mgm. of epinephrine into the thigh muscles at intervals of 15 minutes. Rise in rectal temperature was usually observed within 90 minutes after the first injection of the series and was invariably present at 120 minutes. Fevers rose to a peak 1.0 to 2.5°C. above the baseline within two and one-half to three and one-half hours and fell gradually over an additional period of two or three hours. Temperature curves were monophasic; significant secondary rises such as are commonly seen in rabbits after injection of bacterial pyrogen (17) were not observed. Fig. 1 illustrates typical temperature curves in rabbits after intramuscular epinephrine. Measurements of skin temperature in animals given epinephrine showed an irregular downward trend during the first hour followed by a sharp drop of 8 to 10°C. and sustained hypothermia as rectal temperature rose (Fig. 2).

With *l*-norepinephrine, a similar procedure, employing 0.2 mgm. amounts for each of five intramuscular injections at intervals of 15 minutes, was found to give comparable rises in temperature (Fig. 3).

These dosages of epinephrine and *l*-norepinephrine were employed in all of the experiments to be described.

Effect of Daily Injections of Epinephrine and l-*Norepinephrine*

Repeated injection of bacterial pyrogens at short intervals in rabbits leads to the development of striking resistance or "tolerance" to the fever-producing effect of these materials (17). In order to determine whether daily injections

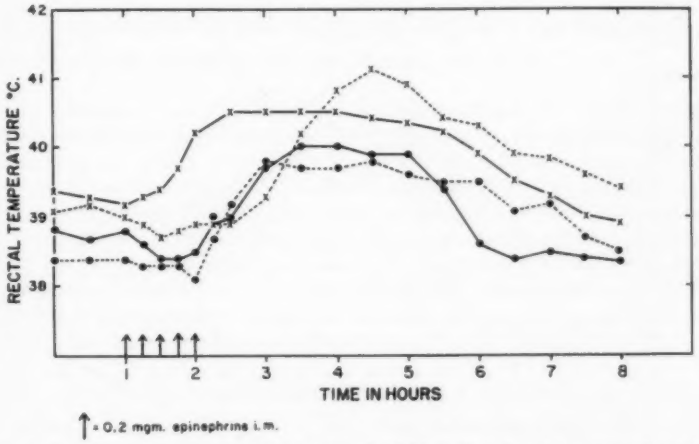

FIG. 1. Rectal temperatures of four normal rabbits after five intramuscular injections of 0.2 mgm. epinephrine at intervals of 15 minutes.

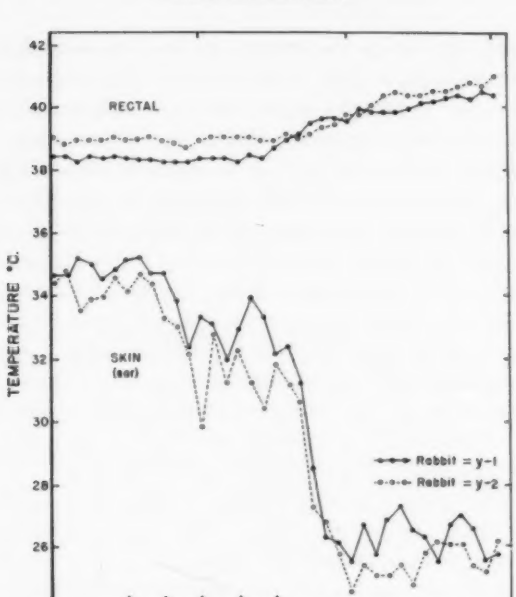

FIG. 2. Simultaneous rectal and skin (ear) temperatures in two rabbits given epinephrine intramuscularly. Note the irregular downward trend of skin temperature during the first hour followed by a sharp drop and sustained lowering at about the time that rectal temperature began to rise.

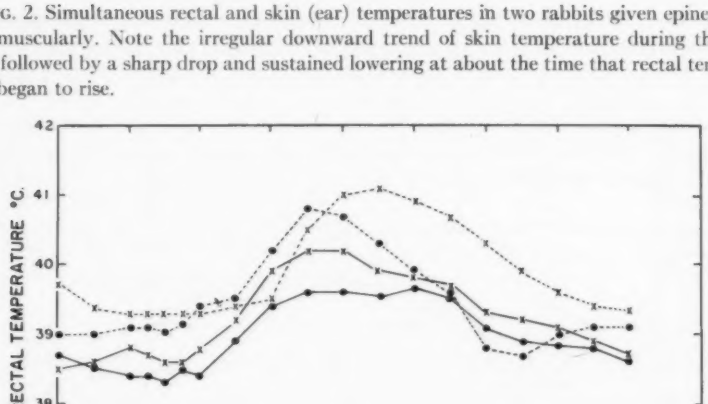

FIG. 3. Rectal temperatures of four normal rabbits after five intramuscular injections of 0.2 mgm. *l*-norepinephrine at intervals of 15 minutes.

TABLE I

Febrile Responses of Normal Rabbits to Daily Injections of Epinephrine

Animals	Fever Index						
	Day 1	Day 3	Day 5	Day 8	Day 10	Day 14	Mean
S-1	46	57	63	78	70	52	61
S-2	88	54	94	108	84	80	85
S-3	49	61	62	77	80	68	66
S-4	82	74	68	94	57	70	74
S-5	65	70	64	92	103	85	79
S-6	96	73	111	108	98	101	98
Mean.....	71	65	77	93	82	76	

TABLE II

Febrile Responses of Normal Rabbits to Daily Injections of l-Norepinephrine

Animals	Fever Index						
	Day 1	Day 3	Day 6	Day 9	Day 12	Day 15	Mean
N-1	27	38	58	26	62	35	41
N-2	91	57	108	77	82	73	65
N-3	32	83	62	54	40	77	58
N-4	67	37	88	73	81	60	68
N-5	111	72	84	94	123	98	97
N-6	63	31	76	57	61	58	58
Mean.....	60	53	79	63	75	67	

of epinephrine resulted in any comparable resistance and lessening of the febrile response, the following experiments were carried out.

Eight rabbits were given five injections of 0.2 mgm. epinephrine daily for 14 days, their rectal temperatures being recorded after this procedure on the first, third, fifth, eighth, tenth, and fourteenth days. Fever curves were drawn and fever indices were determined. It can be seen from the data recorded in Table I that although there was considerable variation among the animals of the group, daily responses for each individual were comparable and there was in no instance any indication of diminishing responsiveness to epinephrine with repeated injections. In a similar experiment, six animals were given *l*-norepinephrine daily and temperature responses were measured on the first, third, sixth, ninth, twelfth, and fifteenth days. As can be seen in Table II, the fevers of individual animals fell within the same range throughout the period of observation.

These experiments were repeated in a group of six rabbits with epinephrine and a group of five rabbits with *l*-norepinephrine with comparable results. No evidence of lessened response, as indicated by measurements of rectal temperature, was found in any animals.

TABLE III

Effect of Injection of Thorotrast Upon Febrile Response of Rabbits to Epinephrine

Animals	Fever Index			
	Day 1	Day 2	Day 3	Day 4*
T-1	24	22	38	28
T-2	79	66	91	66
T-3	94	132	90	102
T-4	47	37	59	53
T-5	67	68	43	71
T-6	72	92	112	80
Mean	64	86	72	67

* 9.0 ml. Thorotrast intravenously 16 hours before injection of epinephrine on Day 4.

Effect of Thorotrast Upon Fever after Epinephrine

Prior injection of Thorotrast or other colloidal materials (17) enhances the febrile response of rabbits to bacterial pyrogens. The effect of Thorotrast upon epinephrine fever was tested in the following experiment.

Six animals received epinephrine daily for three days, their temperatures being recorded and fever indices computed. On the afternoon of the third day, each rabbit was given 9.0 ml. of Thorotrast (colloidal thorium dioxide-Heyden) intravenously and on the fourth day, epinephrine was again administered and fevers recorded. As can be seen in Table III, there was no accentuation of the febrile response to epinephrine by injection of Thorotrast.

Effect of Acquired Resistance to Bacterial Pyrogens Upon Febrile Response to Epinephrine and l*-Norepinephrine*

Tolerance to fever acquired by repeated injections of pyrogen produced by one bacterial species is nonspecific in the sense that the resistance to fever is operative against pyrogens produced by other species (17). To determine the influence of pyrogen tolerance upon the febrile response to epinephrine and *l*-norepinephrine, the following experiments were done.

Six rabbits were given epinephrine daily for three days, their temperatures being recorded each day. Beginning on the fourth day, each animal was given 0.125 ml. of typhoid vaccine intravenously each day for eight days. Temperatures were recorded after vaccine injection on the fourth and again on the eleventh day, at which time tolerance to the typhoid pyrogen was well established. On day 12, epinephrine injection was repeated and temperatures were recorded. There was no evidence of lessened response to epinephrine in animals tolerant to typhoid vaccine (Table IV).

In a similar experiment, five rabbits were tested with *l*-norepinephrine before and again after being rendered tolerant by daily injections of 100 mcgm. of Piromen for nine days. There was no effect of acquired resistance to this pyrogen upon the height of fevers after *l*-norepinephrine (Table V).

TABLE IV

Effect of Acquired Resistance to Bacterial Pyrogen (Typhoid Vaccine) Upon Febrile Response of Rabbits to Epinephrine

Animals	Fever Index					
	Day 1*	Day 2*	Day 3*	Day 4†	Day 11‡	Day 12*
R-1	68	92	54	147	61	77
R-2	81	78	90	123	33	110
R-3	113	87	94	201	28	78
R-4	66	53	71	176	32	66
R-5	31	23	28	89	11	41
R-6	43	71	57	144	41	62
Mean.....	67	67	65	147	34	72

* Epinephrine injected and temperature recorded Days 1, 2, 3, and 12.
† First injection 0.125 ml. typhoid vaccine on Day 4.
‡ Eighth injection 0.125 ml. typhoid vaccine on Day 11.

TABLE V

Effect of Acquired Resistance to Bacterial Pyrogen (Piromen) Upon Febrile Response of Rabbits to l-Norepinephrine

Animals	Fever Index					
	Day 1*	Day 2*	Day 3*	Day 4†	Day 12‡	Day 13*
R-7	37	49	34	97	18	52
R-8	64	80	93	112	41	86
R-9	71	39	54	88	11	47
R-10	89	108	78	74	22	81
R-11	41	43	68	132	31	77
Mean.....	60	64	65	101	25	67

* *l*-Norepinephrine injected and temperature recorded Days 1, 2, 3, and 13.
† First injection of 100 mcgm. Piromen on Day 4.
‡ Ninth injection of 100 mcgm. Piromen on Day 12.

Effect of ACTH Upon Febrile Response to Epinephrine

In order to determine the effect of prior treatment with ACTH upon the febrile response to epinephrine, groups of animals were given intramuscular injections of ACTH in various dosages and their temperature responses were recorded after administration of epinephrine or *l*-norepinephrine.

On the basis of experiments previously reported (4), the following schedules for administration of ACTH were employed as those most likely to modify the febrile response:

Group A—Eight animals given 2.5 units ACTH twice on the first day followed by 2.5 units on the second day immediately before fever testing.

Group B—Eight animals given 5.0 units ACTH twice daily for two days and 5.0 units on the third day immediately before testing.

TABLE VI

Effect of ACTH Upon Febrile Response of Rabbits to Epinephrine

Animals	Fever Index	
	Before ACTH	After ACTH
A-1*	37	44
A-2	61	80
A-3	41	36
A-4	67	59
Mean	51	55
B-1†	111	90
B-2	78	86
B-3	91	79
B-4	66	79
Mean	86	83
C-1‡	42	50
C-2	67	74
C-3	81	72
C-4	38	51
Mean	57	61

* See text for ACTH dosage, Group A.
† See text, Group B.
‡ See text, Group C.

Group C—Eight animals given 10 units ACTH twice daily for seven days and 10 units on the eighth day immediately before testing.

Four animals from each group received epinephrine prior to ACTH treatment and were again given epinephrine after the course of injections of ACTH. Similarly, four animals were tested with *l*-norepinephrine before and after ACTH administration.

The results of these experiments are shown in Tables VI and VII. Although these dosages of ACTH corresponded to those which result in wide variations in pyrogen fever in rabbits, there was no significant change in responses to epinephrine or to *l*-norepinephrine after administration of ACTH.

Effect of Cortisone Upon Febrile Response to Epinephrine

Eight animals were given single intramuscular injections of 25 mgm. of cortisone daily for ten days. Four animals received epinephrine on days 1, 3, 5, 7, 9, and 10 and four were tested with *l*-norepinephrine on the same days. With this dosage of cortisone, animals given single test doses of bacterial pyrogen show progressive diminution in fevers during the first 6–7 days. This initial antipyretic effect then gives way to a gradual increase in febrile responses which is clearly evident as an accentuation of fever by the ninth and tenth days (4).

As can be seen in Table VIII there was no modification of febrile responses in animals given cortisone. This experiment was repeated in a group of four

TABLE VII

Effect of ACTH Upon Febrile Response of Rabbits to l-Norepinephrine

Animals	Fever Index	
	Before ACTH	After ACTH
A-5*	77	66
A-6	91	89
A-7	84	75
A-8	42	51
Mean	76	70
B-5†	77	60
B-6	53	83
B-7	44	36
B-8	94	81
Mean	67	65
C-5‡	77	75
C-6	48	71
C-7	103	114
C-8	86	71
Mean	78	84

* See text for ACTH dosage, Group A.
† See text, Group B.
‡ See text, Group C.

TABLE VIII

Effect of Cortisone Upon Febrile Response of Rabbits to Epinephrine and l-Norepinephrine

Animals*	Fever Index					
	Day 1	Day 3	Day 5	Day 7	Day 9	Day 10
E-1†	48	54	39	62	71	63
E-2	83	72	90	87	49	70
E-3	71	62	85	103	81	75
E-4	47	38	49	29	43	45
Mean	62	56	66	70	61	63
E-5‡	103	74	84	87	88	76
E-6	60	76	63	53	56	70
E-7	57	52	66	49	71	60
E-8	38	47	54	45	63	54
Mean	64	62	67	58	69	65

* Each animal given 25 mgm. cortisone intramuscularly daily for 10 days.
† E-1–E-4 tested with epinephrine.
‡ E-5–E-8 tested with *l*-norepinephrine.

rabbits using 5.0 mgm. of cortisone daily, testing with epinephrine and in a group of three rabbits using 10.0 mgm. of cortisone daily, testing with epinephrine. There was no indication of any effect of these amounts of cortisone upon epinephrine-induced fever in these animals.

DISCUSSION

As has been mentioned, pyrogen fever in the rabbit is primarily a result of decreased heat loss due to peripheral vasoconstriction and there is a certain amount of evidence to indicate that this constriction is mediated by epinephrine-like substances. The present experiments shed no light upon the final role of such substances in pyrogen fever but they indicate clearly that the ability of the cutaneous vessels to constrict in response to administered epinephrine or *l*-norepinephrine is not impaired significantly by ACTH or cortisone in the rabbit. Modification of the febrile response to pyrogen in rabbits by adrenal steroids involves some mechanism other than an alteration of peripheral vascular reactivity to epinephrine and allied substances. Presumably, ACTH and cortisone have their action at some point or points earlier in the chain of events leading to vasoconstriction after pyrogen administration, perhaps in the central nervous system. Experiments designed to test this possibility are underway.

The failure of prior injection of Thorotrast or acquired resistance to bacterial pyrogens to influence the febrile response to epinephrine also indicates that the modification of fever by these means does not directly involve alteration of peripheral vascular responsiveness.

SUMMARY AND CONCLUSIONS

Prior treatment of rabbits with ACTH, cortisone, Thorotrast, or multiple injections of bacterial pyrogen resulted in no modification of fever produced by intramuscular injection of epinephrine or *l*-norepinephrine.

It is concluded that the effects of adrenal steroids upon temperature regulation and the effects of Thorotrast and pyrogen tolerance upon pyrogen fever are not due to alteration of the reactivity of peripheral vessels to epinephrine and allied substances.

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ARTERIAL BLOOD OXYGEN AND CARBON DIOXIDE TENSION STUDIES IN THE RESPIRATORY PARALYSIS OF POLIOMYELITIS

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In the management of patients with respiratory paralysis, it is essential to know the adequacy of alveolar ventilation and to recognize obstruction of the bronchial tree. Although clinical methods are usually effective in discovering these abnormalities, a study of the arterial blood oxygen and carbon dioxide tensions provides a more precise and frequently earlier indication of changes. An understanding of the physiological principles underlying the changes in arterial blood allows a logical and rational approach to treatment.

METHODS

Studies were performed only when it was believed that laboratory aid would elucidate the clinical situation. Arterial blood was drawn and analysed for oxygen tension, carbon dioxide tension and carbon dioxide content by the methods of Riley (1) and Van Slyke (2). pH was determined by the nomogram of Singer and Hastings (3). Some patients were studied in the respirator to determine the state of ventilation and bronchial obstruction. Other patients were studied as they were weaned from the respirator, in an attempt to evaluate the efficiency of respiration.

ALVEOLAR VENTILATION

The volume of gas expired per unit time is made up of the dead space gas (which does not come into contact with blood in the alveolar capillaries) and the alveolar gas (which does come into contact with blood in the alveolar capillaries). If alveolar ventilation is reduced, carbon dioxide tends to accumulate in the blood. The mechanism of this physiological reaction has been discussed elsewhere in detail (4). In poliomyelitis, alveolar ventilation may be reduced because of severe respiratory muscle paralysis, or less often, by paralysis of the respiratory center. If the patient is in a respirator, ventilation may be too little because of slow rate, low pressure or leaks in the respirator. Obstruction of the airways alone, (unless it is generalized as in diffuse pulmonary emphysema) is not a common cause of alveolar underventilation in poliomyelitis. When one finds on examination of the arterial blood, that the carbon dioxide pressure is elevated above 45 mm. of Hg., one may conclude that there is alveolar hypoventilation owing to one of the causes ennumerated

above. If the carbon dioxide pressure is below 35 mm. of Hg. one may conclude that the alveolar ventilation is excessive owing to apprehension (if the patient is breathing spontaneously) or to mechanical overventilation (if the patient is in a respirator). Pressures between 35 and 45 mm. of Hg. are within normal limits and indicate normal alveolar ventilation.

BRONCHIAL OBSTRUCTION

Because of inability to cough and expectorate effectively, the patient with respiratory paralysis may develop airway obstruction secondary to excessive bronchial secretions. Physiologically, bronchial obstruction in its early stages allows mixed venous blood to pass through lung parenchyma which is poorly ventilated. This poorly oxygenated blood causes a lowering of the arterial blood oxygen tension. The assumption that any lowering of the arterial blood oxygen tension below normal limits may be accounted for by shunting of blood through localized poorly ventilated lung areas can only be made if we know that overall alveolar ventilation is adequate or excessive. Since the arterial carbon dioxide pressure is a measure of alveolar ventilation, then one can obtain from the analysis of carbon dioxide and oxygen tensions in the arterial blood an estimation of both alveolar ventilation and blood perfusion of poorly ventilated areas. The latter abnormality is a result of the failure in distribution of ventilation to the areas whose bronchi are blocked by secretions. In short, when Pa_{CO_2} is less than 45 mm. of Hg. (indicative of normal or excessive alveolar ventilation), the Pa_{O_2} is a measure of the adequacy of ventilation to localized lung areas (distribution of ventilation): a high Pa_{O_2} denotes homogeneous distribution; a low Pa_{O_2} denotes inhomogeneous distribution. These relationships have been exhaustively discussed in the publications of Riley (5).*

Table I shows the various possibilities which may exist in any patient and the physiological and clinical conclusions to be drawn from the findings.

* In simplified form, the equation for alveolar oxygen tension is:

$$P_{A_{O_2}} = 150 - \frac{Pa_{CO_2}}{R.Q.} \qquad (6)$$

If we assume an R.Q. between .7 and 1.0, we see that when Pa_{CO_2} is normal (40 mm. of Hg) $P_{A_{O_2}}$ never drops below 90 mm. of Hg. Since the average oxygen gradient between $P_{A_{O_2}}$ and Pa_{O_2} is 10 mm. of Hg, a Pa_{O_2} below 80 mm. of Hg. may be assumed to be abnormal. Pa_{O_2} values between 80 and 90 mm. of Hg. are borderline and above 90 mm. of Hg are normal.

$P_{A_{O_2}}$ = Alveolar oxygen tension.

Pa_{O_2} = Arterial oxygen tension.

Pa_{CO_2} = Arterial carbon dioxide tension.

In addition to the determination of Pa_{O_2} and Pa_{CO_2}, the determination of carbon dioxide content and hematocrit allows calculation of the buffer base and pH. From these values one may estimate whether the process is acute or chronic in nature (4).

RESULTS

Case 1: (C. L. 173096) This 20 year old white automobile mechanic developed severe spinal and moderate bulbar paralysis on August 5, 1953. There

TABLE I

The Various Possible Arterial Blood Oxygen and Carbon Dioxide Tension Findings in Poliomyelitis Patients and Their Physiological and Clinical Interpretation

Pa_{CO_2}	Pa_{O_2}	Physiological Situation		Probable Clinical Situation	
		Alveolar Ventilation	Distribution of air throughout the lungs	Ventilation	Airway Patency
34–45	90+	Normal	Normal	Normal	Normal
35–45	80–*	Normal	Localized poorly ventilated lung areas are present	Normal	Localized bronchial obstruction and/or bronchopneumonia and atelectasis†
35–	90+	Increased	Normal	Overbreathing owing to anxiety or excessive mechanical ventilation	Normal
35–	80–	Increased	Localized poorly ventilated lung areas are present	Same as above	Localized bronchial obstruction and/or bronchopneumonia and atelectasis†
45+	90+	Reduced	Normal	Under ventilation owing to respiratory center paralysis, respiratory muscle weakness or inadequate mechanical ventilation	Normal
45+	80–	Reduced	Localized poorly ventilated lung areas cannot be detected in the presence of severe general alveolar underventilation	Same as above	Localized bronchial obstruction cannot be detected in the presence of severe general alveolar underventilation

* The lower normal limit for Pa_{O_2} is not as clear as that for Pa_{CO_2}. (See footnote)

† Wherever bronchial obstruction exists, atelectasis and bronchopneumonia are usually present also.

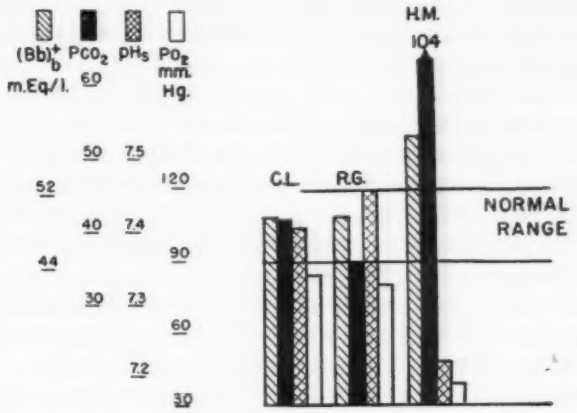

FIG. 1. Buffer base, Pa_{CO_2}, pH and Pa_{O_2} in three patients (C. L., R. G. and H. M.). Note that in the figures a Pa_{O_2} of 90 mm. of Hg. is given as the lower limit of normal. Under unusual circumstances 80 mm. of Hg may be normal.

was diplopia, difficulty in swallowing and poor action of the intercostal muscles. He was unable to cough and his speech was nasal. There was weakness of both deltoid muscles and of the left leg. A tracheotomy was done on admission, and he was placed in an Emerson respirator. The respiratory muscles were never completely paralysed, and within a week he was able to be out of the respirator for several hours at a time. At discharge for rehabilitation, there was slight weakness of the abdominal muscles with spotty involvement of the shoulder and arm muscles.

Comment: Studies were done on this patient on the morning following admission, when he had been in respirator overnight. Buffer base, Pa_{CO_2} and pH were normal (Fig. 1). Pa_{O_2} was slightly low, but not sufficiently low to suggest any major bronchial obstruction. It was concluded that ventilation was adequate and that no evidence of bronchial obstruction existed.

Case 2: (R. G. 172964) This 28 year old white man entered Baltimore City Hospitals August 1, 1953 complaining of headache and neck stiffness of one day's duration.

The temperature was 101° F., the neck was stiff, but there was no other localizing sign.

The spinal fluid contained 168 mgm. per cent of protein and 280 cells of which 75 per cent were polymorphonuclear.

On the morning following admission, paralysis of both legs and retention of urine became manifest. On the second hospital day, respiratory difficulties became apparent. A tracheotomy was performed, and the patient was placed in an Emerson respirator.

He did well in the respirator and was transferred for rehabilitation on September 8, 1953. At this time there was paralysis of both legs. The respiratory muscles had apparently improved.

Comment: The arterial blood study done just before the patient was placed in the respirator on August 3, showed that there was adequate alveolar ventilation (Fig. 1). Pa_{O_2} was at low levels (81 mm. of Hg.) although there was no clinical evidence of increased secretions or bronchial obstruction.

Case 3: (H. M. 174491) This 24 year old white man was admitted to the Baltimore City Hospitals on September 10, 1953 complaining of malaise, fever, and neck stiffness of 2 days' duration.

Examination showed a temperature of 101.6° F., nuchal rigidity, a positive Kernig's sign. Spinal fluid showed a protein of 72 mgm. per cent, 424 cells per cubic millimeter of which 95 per cent were polymorphonuclear.

On the third day, respirations became rapid and shallow. A left facial paralysis, bilateral weakness of the upper extremities and an increase in intercostal weakness were noted. Tracheotomy was performed, and the patient was placed in an Emerson respirator. Despite penicillin and streptomycin he ran a high fever. The paralysis extended to include all four extremities. On the sixth hospital day, he began to have difficulty with expectoration of thick mucous. Despite repeated bronchoscopy with continuous suction, he continued to get worse and died on the eighth hospital day. An arterial blood study was performed about 10 minutes prior to death.

Post-mortem examination (Dr. Lukens) showed the presence of a tracheotomy wound and a patent track into the tracheal lumen. There was collapse of the right upper and lower lobes with partial collapse of the right middle lobe. The left lower lobe was also collapsed. The trachea and major bronchi were almost completely filled with extremely thick tenacious yellow mucopurulent secretions. The left upper lobe contained air, but showed considerable edema. The left lower and right upper lobes were completely atelectatic and edematous. The right middle lobe was partially atelectatic. There was confluent bronchopneumonia of the right lower lobe. The examination was not otherwise remarkable.

Comment: The study done just prior to death showed an extremely high Pa_{CO_2} and a very low Pa_{O_2} (Fig. 1). The high Pa_{CO_2} demonstrated severe alveolar hypoventilation. Buffer base was also elevated with a low pH strongly suggesting that the alveolar hypoventilation was of sufficient duration to allow some compensation by renal mechanisms. These facts can be ascertained from interpretation of the blood findings alone, and are in agreement with the clinical course. The cause of the alveolar hypoventilation in this case was probably diffuse bronchial obstruction with atelectasis of both lungs making expansion of the lungs by mechanical means impossible. The low Pa_{O_2} cannot be as clearly interpreted because the Pa_{CO_2} was elevated.

Case 4: (H. W. 172940) This 28 year old housewife was admitted to the Baltimore City Hospitals on July 31, 1953 with a history of fever and muscle pains of two days' duration, followed by difficulty swallowing, regurgitation of food, and inability to cough.

The temperature was 104° F. There was difficulty swallowing, poor movement of the palate, and weakness of the right sternocleidomastoid muscle. The spinal fluid showed 104 lymphocytes per cubic mm. and a 4 plus Pandy.

Because of very shallow breathing and inability to control secretions, a tracheotomy was performed, and the patient was placed in a respirator on August 3. Thick purulent material was obtained from the tracheotomy tube. On August 4 there was an episode of mental confusion. An arterial blood study was performed at this time. Over the next several days there was gradual improvement. Arterial blood studies were repeated on August 7 and 10, two days after removal from the respirator. She continued to have some excessive purulent discharge from the tracheotomy tube for a week thereafter.

Comment: Figure 2 depicts the serial studies performed in this patient. The study done during the episode of mental confusion showed severe alveolar hyperventilation. A study done on August 7 was nearly normal. The study of August 10 showed a slightly depressed Pa_{O_2} thought to be caused by respiratory obstruction secondary to the excessive secretions she continued to have after removal from the respirator.

Case 5: (H. M. 174683) This 22 year old white woman was admitted to the Baltimore City Hospitals on September 17, 1953 complaining of muscle aches, headache, and vomiting for 3 days with arm weakness of ten hours' duration.

Examination showed a temperature of 99.6° F., rapid, shallow respirations with maximal use of accessory muscles of respiration. There was a flaccid

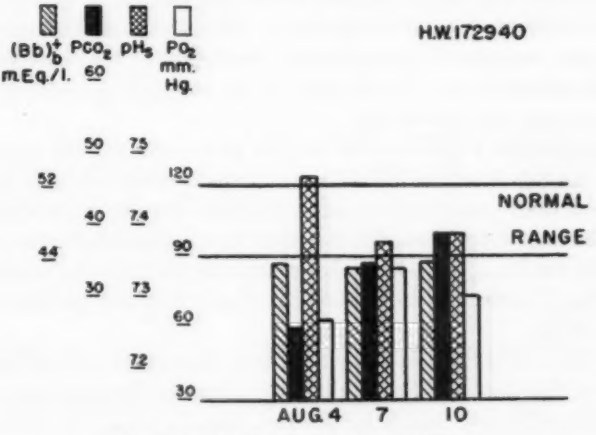

FIG. 2. Serial studies on blood of Case 4.

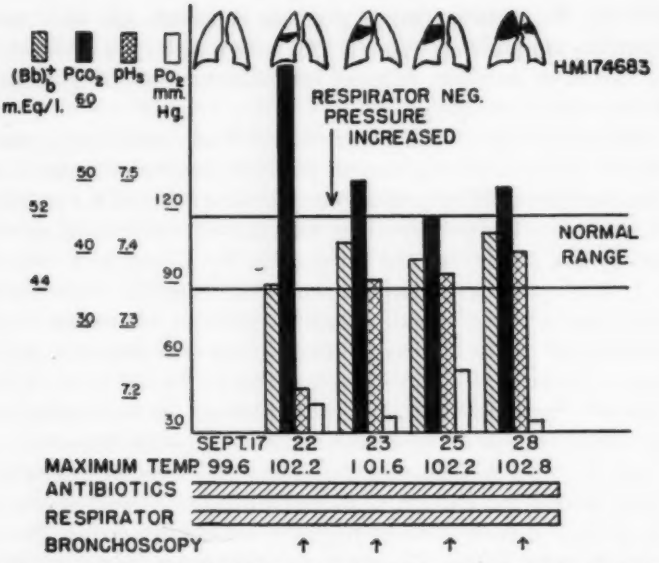

FIG. 3. Serial studies on blood of Case 5, showing tendency toward alveolar underventilation, and low Pa_{O_2} associated with bronchial obstruction, atelectasis and pneumonia.

paralysis of the right arm and definite weakness of the muscle groups of the left arm. Lumbar puncture yielded clear fluid containing 93 cells per cubic millimeter of which 90 per cent were lymphocytes.

A tracheotomy was done, and the patient was placed in a respirator. Her temperature rose and remained elevated throughout the hospital course. There was rapid loss of all function of the extremities as well as loss of the ability to swallow. Despite antibiotics, continuous suction and repeated bronchoscopy, an area of consolidation developed in the right lung and inexorably increased in size. On October 3, she suddenly became cyanotic and died. No autopsy was performed.

Comment: Figure 3 indicates the studies performed. At the top of the diagram, the finding of consolidation in the lungs is indicated. The initial study showed that there was a high Pa_{CO_2} indicating alveolar hypoventilation. Increasing the negative pressure in the respirator improved alveolar ventilation and brought the Pa_{CO_2} down toward normal as shown in the subsequent studies. The low Pa_{O_2} is indicative of bronchiolar obstruction and perfusion of poorly ventilated areas.

Case 6: (R. F. 175298) This 28 year old draftsman came to the Baltimore City Hospitals on October 3, 1953 complaining of malaise for one week, with back stiffness, anorexia and headache for one day.

Examination was not remarkable except for a temperature of 104° F. and nuchal rigidity. The spinal fluid contained 132 cells per cubic mm. of which 85 per cent were lymphocytes. The spinal fluid protein was 110 mgm. per cent.

During the first day, marked weakness of both legs with rapid progression to include both arms occurred. On the morning of the second hospital day, breathing was almost purely diaphragmatic, with little intercostal activity. At this time a tracheotomy was performed, and the patient was placed in a respirator. Over the next few days there was loss of ability to swallow. The uvula became paralysed. There was evidence of poor aeration of the lung, and bronchoscopy was done on the seventh hospital day. Several mucous plugs were removed, and he appeared improved. During the next three weeks he remained in critical condition.

By December, 1953, he had improved sufficiently to be tried out of the Emerson respirator in the Monaghan respirator. At this time he had no use of his legs, slight function in the hands, but no use of the shoulders or upper arms. Breathing was performed mainly with accessory neck muscles, although there was slight use of poorly functioning intercostal muscles. In this condition he was transferred to another hospital for rehabilitation.

Comment: Figure 4 shows the three studies performed on this patient. The study of October 12 was done several days after the episode of poor lung aeration necessitating bronchoscopy. The study showed that alveolar ventilation was slightly increased, but that Pa_{O_2} was low, suggesting bronchial blockage by secretions.

The study of February 5 was done while the patient was in the Monaghan

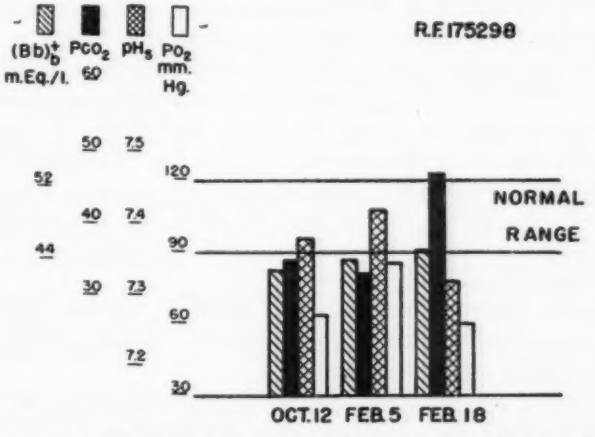

FIG. 4. Serial studies on blood of Case 6, showing (Feb. 18) tendency to develop acute respiratory acidosis when removed from mechanical respirator for a short period.

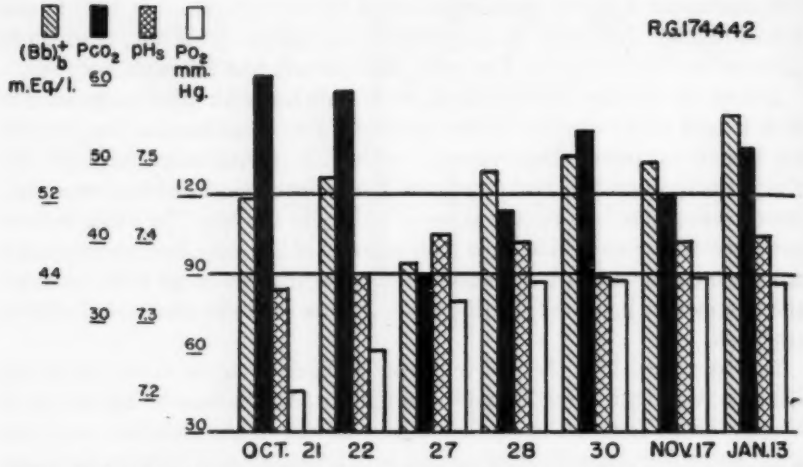

FIG. 5. Serial studies on blood of Case 7, showing respiratory acidosis on Oct. 21 and 22, when patient was out of respirator. Study on Oct. 27 done after patient had been in respirator overnight. Studies of Oct. 28 and 30 show development of respiratory acidosis after being kept out of respirator one and three days respectively.

respirator and showed that alveolar ventilation was increased and Pa_{O_2} at low normal values.

The last study was done to evaluate his spontaneous ventilation. After having been in the Emerson respirator overnight, he was placed in the Monaghan. He was allowed to breathe spontaneously for three-quarters of an hour. He was then placed in the Monaghan for 15 minutes. Spontaneous breathing was again allowed, and the blood specimen drawn for analysis after 5 minutes. This study showed that the patient was unable to maintain adequate alveolar ventilation for 5 minutes. The fall in oxygen tension during the same time is difficult to interpret as pointed out above, but was probably owing to severe general alveolar underventilation. Because of this objective demonstration of inadequate ventilation, the patient's weaning from the respirator was slowed.

Case 7: (R. G. 174442) This 25 year old white man was admitted to the Baltimore City Hospitals on September 9, 1953 with malaise of 1 week's duration and respiratory difficulty for one day.

Examination showed a temperature of 102.4° F., shallow breathing with only slight intercostal movement. The spinal fluid contained 144 cells per cubic mm. and 110 mgm. per cent of protein.

A tracheotomy was performed, and the patient was placed in a respirator. During the next few days he developed a quadraplegia.

On the thirteenth hospital day, he was taken out of the respirator for 15 minutes, and the time out of the respirator was gradually increased over the

next four months. During this time there was some improvement in extremity motion, and, at the time of discharge, he no longer needed the respirator. He was able to walk across the room in his braces. He was transferred to another hospital for further rehabilitation on January 29, 1954.

Comment: This patient had such severe loss of respiratory muscles, that he was unable to maintain adequate alveolar ventilation for months after paralysis (Fig. 5). The studies performed on October 21 and 22 when the patient had been out of the respirator for several hours, showed that the Pa_{CO_2} was high, suggesting alveolar underventilation probably owing to respiratory muscle tiring. At the same time it will be noted that the buffer base was nearly normal and the pH was low, suggesting that there had been insufficient time for the respiratory acidosis to become compensated by the renal mechanism. The Pa_{O_2} was low in both these studies, but cannot be evaluated in terms of location of the increased oxygen pressure gradient. From October 22 to October 27, the patient was kept in the respirator continuously. The physiological result was the return of the buffer base, Pa_{CO_2}, pH and Pa_{O_2} to normal values.

The patient was then allowed out of the respirator during the next several days, and studies were repeated on October 28 and October 30. These studies showed the gradual development of respiratory acidosis.

A study done on November 17, when the patient had been out of the respirator for one day resembled the previous study (October 28) done under the same conditions.

A final study performed on January 13 after the patient had been out of the respirator for about one month showed a state of compensated respiratory acidosis with normal arterial blood oxygenation.

DISCUSSION

Some changes in Pa_{O_2} and Pa_{CO_2} which occur with respiratory muscle paralysis have been described above. The interpretation of these findings in terms of physiological and anatomical terms has been indicated.

Certain generalizations may be made from examination of the material presented here.

1. Oxygen tensions: In no case studied was the oxygen tension of the arterial blood at high levels. In many, it was within the normal range, but always low normal. When the Pa_{O_2} is low in the presence of a normal or low Pa_{CO_2}, generalized alveolar underventilation can be eliminated as the cause of the low Pa_{O_2}. This leaves localized underventilation or inhomogeneous ventilation as the most likely cause of the low Pa_{O_2}. Where excessive secretions are present in the bronchial tree, one may assume that the localized underventilation is secondary to bronchial obstruction. If there are no secretions, the possibility of inhomogeneous ventilation owing to unequal muscle paralysis on the two sides of the chest must be considered. Under these circumstances it might be

possible to ventilate one area of the lungs where muscle function is good, without moving any air into a portion of the lung where thoracic muscle and the diaphragm are non-functional.

2. The development of chronic respiratory acidosis in patients with inadequate ventilation: Two patients (R. F. and R. G.) were unable to ventilate sufficiently to maintain a normal Pa_{CO_2} several months after the acute stage of their disease. The existence of respiratory acidosis in these patients was not suspected until the arterial blood studies were done. In one patient (R. G.) it was possible to follow the development of respiratory acidosis over two days (Fig. 5, October 28 to 30) after removal of the patient from the respirator. The Pa_{CO_2} rose gradually over a three day period and then presumably leveled off around 54 mm. of Hg.

The final value of Pa_{CO_2} depends on the effectiveness of the remaining respiratory muscles. If they are unable to ventilate the lungs sufficiently, the Pa_{CO_2} will rise and produce through the respiratory center the signal for increased ventilation. If the respiratory muscles are unable to respond, the Pa_{CO_2} will remain elevated (7). The compromise, although not a complete compensation (8), is adequate for long life, and occasionally may not be detected except by special tests.

SUMMARY

Analysis of the arterial blood for oxygen and carbon dioxide tensions provides valuable information about alveolar ventilation and the distribution of ventilation in patients with respiratory muscle paralysis secondary to poliomyelitis. Various abnormalities of these values in a group of patients with poliomyelitis are reported and discussed.

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HERMAPHRODITISM, GENDER AND PRECOCITY IN HYPERADRENOCORTICISM: PSYCHOLOGIC FINDINGS*

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Supported by a generous research grant from the Josiah Macy, Jr. Foundation, Dr. Joan G. Hampson and I, recently accompanied by Dr. John L. Hampson, have for three years been making a psychologic investigation of patients with adrenocortical and other sexual anomalies, at The Johns Hopkins Hospital.†

There are two aspects of congenital hyperadrenocorticism that are of major psychologic interest, namely, hermaphroditism in the females, and virilizing precocity in both males and females.

HERMAPHRODITISM

The psychologic pertinence of hermaphroditism in human beings is that it provides illuminating evidence concerning the determinants and concomitants of sexual outlook and orientation. The evidence is most illuminating if hyperadrenocortical hermaphrodites are considered not in isolation, but in connection with other varieties of hermaphrodite. By the term, hermaphrodite, is meant a person who congenitally possesses an atypical mixture of male and female elements in the reproductive system, so that their somatic status as male or female is ambiguous. All told, we have studied and followed 60 hermaphroditic patients, ranging in age from birth to fifty.‡ Each of seven different varieties‖ of hermaphroditism has been represented by at least one patient (Table I).

In the fifth variety of hermaphroditism, mixture of male and female elements in the reproductive system is concealed. In the other six varieties, visible signs of ambisexual body morphology are quite evident at birth. Some of the patients in these six categories were assigned to the sex which contradicted their gonadal and, so far as is known, their chromosomal sex.

* Read at the thirteenth M & R Pediatric Research Conference, A Symposium on Adrenal Function in Infants and Children, at the State University of New York, Upstate Medical Center, Syracuse, N. Y., November, 1954.

† The project is under the aegis of John C. Whitehorn, Professor of Psychiatry, The Johns Hopkins University, and of Lawson Wilkins, Associate Professor of Pediatrics, Acting Pediatrician-in-Chief, director of pediatric endocrinology at The Johns Hopkins Hospital.

‡ The method of psychologic investigation was the same as reported elsewhere (1).

‖ The seven varieties were differentiated after a study of more than 300 cases of hermaphroditism reported, in English, in the literature of the last half century (2).

TABLE I

*Varieties of Hermaphroditism**

1. Congenitally hyperadrenocortical female	39
2. Female, with well differentiated phallus, normal ovaries and normal internal reproductive structures	2
3. True hermaphroditism	1
4. Male, with unarrested mullerian differentiation:	
(a) with normal penis and one or both testes cryptorchid	0
(b) hypospadiac and cryptorchid	3
5. Simulant female, with testes, blind vagina, mullerian vestiges and breasts	2
6. Cryptorchid male hypospadiac, with breasts at puberty:	
(a) with urogenital sinus	3
(b) with blind vaginal pouch	0
7. Cryptorchid male hypospadiac:	
(a) with urogenital sinus	8
(b) with blind vaginal pouch	2
	60

* The varieties of hermaphroditism listed in this table, with the exception of the third, have been traditionally referred to as pseudohermaphroditism, male or female. In conformity with tradition, the term, pseudohermaphrodite, is used in several places in the text.

The cases of contradiction between gonadal sex and sex of rearing are tabulated in Table II, together with data on endogenous hormonal sex and gender role. The term gender role is used to signify all those things that a person says or does to disclose himself or herself as having the status of boy or man, girl or woman, respectively. It includes, but is not restricted to sexuality in the sense of eroticism.

Of the 17 people represented in Table II, all but 3 disclosed themselves in the gender role fully concordant with their rearing though contradicted by their gonads. Gonadal structure per se proved a most unreliable prognosticator of a person's gender role and orientation as man or woman; assigned sex proved an extremely reliable one.

Determination of chromosomal sex was not performed routinely on each patient, but preliminary evidence clearly indicates that chromosomes bear as little relationship to sexual orientation as do gonads. Further evidence in support of this contention is the recent discovery that many patients with gonadal agenesis, formerly regarded as females with ovarian agenesis, bear male sex chromosomes. The femininity of these people is indisputable, and has at no time been called to question by any of the physicians dealing with them.

To consider now the relationship between hormonal sex and gender role: hormonal sex must be distinguished from gonadal structure, for ovaries do not always make estrogens, nor testicles androgens. The ovaries of hyperadrenocortical female pseudohermaphrodites are inert and, though the adrenals

TABLE II

Gonads and Rearing Contradictory

17 Cases

Gonads	Endogenous Hormonal Sex	Assigned Sex and Rearing	Gender Role	Type of Hermaphroditism
♀	2 ♀	2 ♂	2 ♂	♀ with ovogenesis
♀	3 ♂	3 ♂	3 ♂	♀ hyperadrenocortical
♂	2 juv. 1 ♂	3 ♀	3 ♀	♂ cryptorchid hypospadiac with mullerian organs
♂	1 juv. 4 ♂	5 ♀	2 ♀ 1 ♀ → ♂ 2 ♂	♂ cryptorchid hypospadiac
♂	2 juv.	2 ♀	2 ♀	♂ cryptorchid hypospadiac with breasts
♂	1 juv. 1 ♀	2 ♀	2 ♀	♀ simulant

produce an excess of estrogens as well as of androgens, androgenic activity dominates and the body is excessively virilized. The testes of male pseudohermaphrodites of the simulant female variety produce estrogens which feminize the body.

Corrective and replacement therapy with endocrine medication has a long enough history that it is rare these days to find hermaphrodites who have lived for several years with a body morphology that grossly contradicts the gender according to which they live. The significant exception is in the case of hyperadrenocortical female pseudohermaphrodites for whom cortisone therapy is new: we have studied seven adult patients who had lived for 20, 23, 30, 34, 37, 45, and 47 years, respectively, before receiving therapy for this disorder. Despite their exaggeratedly virilized bodies, the seven had always lived as women, two of them married, and were entirely feminine in their outlook and ways.

Table III summarizes data on the 27 individuals who went through and beyond a puberty—or, in the case of hyperadrenocorticism, a precocious puberty-equivalent—in which hormonal influences produced a body morphology contradictory of the sex in which they were living. Subsequently the contradiction was corrected with hormonal therapy and, where indicated, with plastic surgery. Psychological data were gathered before treatment, when possible, otherwise retrospectively.

The data of Table III show that of the 27 individuals whose hormonal functioning and secondary sexual body morphology contradicted their as-

TABLE III

Hormonal Sex and Rearing Contradictory

27 Postpubertal Cases

Endogenous Hormonal Sex	Gonads	Assigned Sex and Rearing	Gender Role	Type of Hermaphroditism
♀	♀	2 ♂	2 ♂	♀ with ovogenesis
♀	♂	1 ♂	1 ♂	♂ cryptorchid hypospadiac with breasts
⚥	⚥	1 ♂	1 ♂	true hermaphrodite
♂	♀	18 ♀	17 ♀ 1 ⚥	♀ hyperadrenocortical
♂	♂	1 ♀	1 ♀	♂ cryptorchid hypospadiac with mullerian organs
♂	♂	4 ♀	1 ♀ 1 ♀ → ♂ 2 ⚥	♂ cryptorchid hypospadiac

signed sex, only 4 became ambivalent with respect to gender role, as male or female. All 4 had been reared as girls. One, a cryptorchid hypospadiac male, ran away from home on his own initiative at the age of sixteen and changed from living as a girl to living as a boy. Twenty-one years later, though he had been castrated on account of gonadal malignancy, he was very half-hearted about taking methyl testosterone. He had dissolved a marriage and had three times gone on a last-minute alcoholic binge instead of carrying through with a scheduled hospital admission for hypospadiac repair.

The second of these ambivalent people, was a cryptorchid hypospadiac male with clitoral-sized phallus, blind vaginal pouch and eunuchoid body build. Though she was raised as a girl, she was expected to be a tomboy because genitally she resembled her sister whose condition had been medically diagnosed. At twenty-one, she knew the details of her case with textbook exactitude, and had concluded that she was "a kind of it" who had to take the part of a woman. Her body build and low-pitched voice, along with her mechanical and scientific interests and her dreams and daydreams of intimacies with other girls, she construed as evidence that she "must be a queer." In her dreams, her genitalia were female, not male. She had hopes that surgical lengthening of the vagina, which operation she underwent, and estrogen medication would "make her think like a normal woman."

The third ambivalent person was morphologically a replica of the second. She had been nicknamed a tomboy in childhood by her family. In preadolescence she had played at intercourse with boys a couple of times, and at masturbation with girls on a few occasions. In her middle teens she was medically

diagnosed a gonadal male and knew that a change of sex was in the air. Privately she wanted strongly to remain living as a girl, but the decision was in the hands of the doctors. Eventually she was gonadectomized and given a course of estrogen substitution therapy. After several years on estrogen intermittently, she was so well feminized that she let treatment lapse. She tabooed sexual practices until her late twenties, and thereafter had a transient erotic liaison on two occasions with the same woman and once with a man. Some of her erotic fantasies were homosexual, but she emphatically considered herself not to be a real lesbian. She was extremely successful in her career and planned to postpone marriage, which she desired, until the late thirties, in order to sidestep possible problems consequent on her infertility.

The fourth ambivalent person, a female with congenital hyperadrenocorticism, had received plastic surgery of the genitals in infancy, but grew up with an otherwise virilized body morphology. She was highly gratified with feminization induced with cortisone, and in adulthood requested vaginoplasty to facilitate heterosexual intercourse. In middle childhood, she had been inducted into homosexual relations with an older girl, and continued to have occasional homosexual liaisons after female hormonal functioning had been established. She regarded herself unequivocally as a woman, but one with bisexual inclinations.

Disallowing the fact that these four cases are only four out of twenty-seven, the nature of hormone functioning in each instance was such that they do not offer very convincing evidence of a direct causal relationship between hormonal sex and gender role.

To say that hormonal functioning is not a direct, automatic determinant of either maleness or femaleness of gender role is not to underestimate the linkage between hormonal functioning and gender role. The first link is that hormonal functioning plays a major part in embryonic sexual differentiation of both internal accessory reproductive structures and external genitalia. And it goes without saying that the external genitals are the sign from which parents and others take their cue in assigning a sexual status to a neonate and in rearing him thereafter, and the sign, above all others, which gives a growing child assuredness of his, or her gender. The extraordinary importance of an unequivocal assuredness of gender in hermaphroditic children is taken up in the accompanying companion paper.

The second link is that hormonal functioning plays the major part in establishing secondary sexual characteristics of the body at puberty. These pubertal changes are signs which either reinforce or lessen a child's assuredness of his, or her gender. The importance of pubertal signs is made evident in investigation of eunuchnoid boys and girls with gonadal agenesis. These patients are often desperate in their desire to get the bodily signs of maturity. Without them, the youngsters are not only affected adversely in lowered morale and

self-esteem, but also are deprived of a host of encounters and transactions with age-mates which are indispensable to psychological and social growth toward maturity. Incongruous secondary sexual development, as happens in some hermaphrodites and in boys with gynecomastia, is equally deleterious in its effects. The more publicly visible the incongruity, the more distressing the person finds it. Without exception, hirsute girls and women with the adrenogenital syndrome have said that, more than anything else, they would like to be rid of mustache and beard. The hyperplastic clitoris is second choice, unless the deep-pitched voice is given precedence.

The third link between hormonal functioning and gender role applies to the specifically genital erotic aspects of gender. In hermaphroditism, incongruities between external genital morphology and hormonal functioning may occur, namely, a phallus plus active estrogens but not androgens, and a vagina plus active androgens but not estrogens. Only 10 of our patients who exemplified such incongruity (3 in the first category, 7 in the second) were experienced enough in genital practices to give instructive information. Four of them—all women with the adrenogenital syndrome—were available for interviewing before any corrective procedures, hormonal or surgical were carried out; the others gave retrospective information to the best of their ability. Despite the meagerness of data, it appears that either androgens or estrogens will induce intensification of genital sensations and feelings, regardless of external genital morphology. Without one or the other, physical libido is weak, with them it is more intense. Though growth and function of the phallus is promoted by androgen, and of the vagina by estrogen, neither hormone has exclusive prerogative in dictating masculine or feminine location of genital sensation and gratification.

Chromosomal, gonadal, hormonal, and assigned sex, each of them interlinked, have all come under review as indices which may be used to predict an hermaphroditic person's gender—*his* or *her* outlook, demeanor, and orientation. Of the four, assigned sex stands up as the best indicator. Apparently, a person's gender role as boy or girl, man or woman, is built up cumulatively through the life experiences he encounters and through the life experiences he transacts. Gender role may be likened to a native language. Once ingrained, a person's native language may fall into disuse and be supplanted by another, but it is never entirely eradicated. So also a gender role may be changed or, resembling native bilingualism may be ambiguous, but it may also become so deeply ingrained that not even flagrant contradictions of body functioning and morphology may displace it.

PRECOCIOUS GROWTH AND DEVELOPMENT

Among 51 congenitally hyperadrenocortical patients investigated, male and female, there were 22 who were under study at an age when their precocity was in the ascendant. The group was composed as follows:

TABLE IV

Hyperadrenocortical Precocity

1. Boys who made a quick transition into normal puberty after adrenocortical supression with cortisone between the ages of 5 and 11	6
2. Boys whose precocity was arrested with cortisone between the ages of 3 and 5	4
3. Girls whose virilizing precocity was arrested with cortisone between the ages of 5 and 11	8
4. Girls whose virilizing precocity was arrested with cortisone between the ages of 3 and 5	2
5. Females under 11, living as boys with their virilizing precocity unarrested	2
	22

Brevity in reporting investigations of psychological development is jeopardized by the lack, except for intelligence tests, of suitable brief, concise operations and procedures to employ in collecting data. With the transcripts of recorded interviews and the notes on behavior filed away for reference, let it be said simply that they document this statement: children whose bodily development is precocious are not, de facto, precocious in their psychological development. They develop in step with their contemporaries with the one exception that, being bigger and stronger than their contemporaries, they can move their limbs more powerfully and may, under facilitating circumstances, outstrip them in mastery of physical, muscular operations.

One of the facilitating circumstances that may permit physically precocious children to outstrip their age-mates in various operations of mastery is the possession of a high level of intelligence. Indeed, if the IQ rating does not contraindicate, it is advantageous to accelerate school progress in cases of extreme physical precocity in early childhood, with a view to promoting psychological precocity, and thereby to enable a child to mix and compete socially with others of his own physique.

The 22 children under consideration achieved, with four exceptions, IQ ratings of average or better (Table V). A disproportionate number had an IQ over 110. Unlike congenital hypothyroidism, congenital hyperadrenocorticism does not have an adverse effect on IQ, complications of hermaphroditism and precocity notwithstanding.

In a randomly selected group, one expects IQ levels to conform to a normal curve of distribution. Table VI and Figure 1 compare the proportion of cases expected, in each of seven IQ categories, with the proportions actually obtained.* The disproportionately high percentages in the upper IQ levels may signify either that patients with adrenogenital precocity tend to have high IQs in comparison with a randomly selected group, or that this group of patients was not randomly selected. The latter alternative must be seriously

* It is statistical malpractice to mix IQ scores from the Revised Stanford-Binet test with those from the Wechsler Intelligence Scales. It has been done, nonetheless, for want of an alternative way out.

TABLE V

IQ Findings: 51 Congenitally Hyperadrenocortical Cases

Age cortisone begun	Age tested	IQ			Notes
		Females	Males	Females living as boys	
2–18 mo.	Too young	5 cases	1 case		Physical precocity inhibited in infancy
2–18 mo.	2–5 yr.	100 108 113 121 132 died			Rev. Stan.-Binet IQ
3–5 yr.	3–5 yr.	defec. 96	defec. 131 138* 140	111	Physical precocity in evidence Under 5 yr., Rev. S-B IQ; over 5 yr., Wechsler IQ
5–11 yr.	5–12 yr.	76 100 112 115 122 126 132 136	104 109 110 116 117 125	119	* Tested at 6 yr.
12–17 yr.	12–18 yr.	92 99 102 119 120 127	104	74	Beyond the age of physical precocity Wechsler IQ
18–50 yr.	19–50 yr.	106 108 122 127 140 no data, 4 cases			

TABLE VI

IQ Level: Percentage Distribution

IQ Level	Below 69	70–79	80–89	90–109	110–119	120–129	130–
Expected % of cases	2.2%	6.7%	16.1%	50.0%	16.1%	6.7%	2.2%
Obtained % of cases							
All 40 cases tested	5.0%	5.0%	0.0%	30.0%	22.5%	20.0%	17.5%
22 precocious children only	9.1%	4.5%	0.0%	18.2%	31.8%	13.6%	22.7%

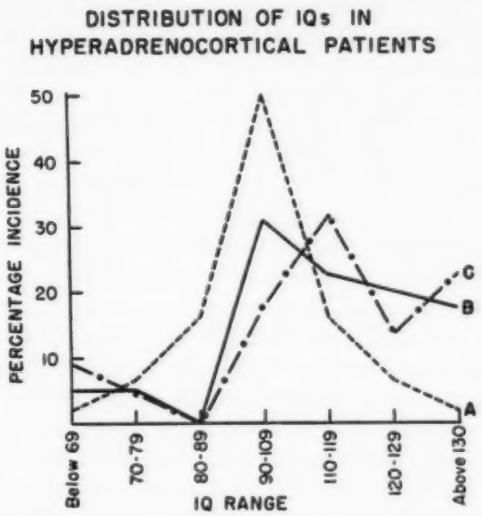

FIG. 1. A. Expected, normal curve distribution. B. All 39 cases tested. C. 22 children tested while physical precocity was evident.

considered, for patients admitted to The Johns Hopkins Hospital are not statistically a random sample of the nation's hospitalized patients.

It is possible that some of the children of high IQ had in some way been facilitated by their precocity in gaining an advantage over nonprecocious children with respect to the information and skills sampled in an IQ test. But there was no explicit confirmatory evidence that this had been so, and one must be wary of jumping to conclusions from the statistics of a small sample. The listings of Table V suggest that high IQ is not peculiarly characteristic of adrenocortical precocity. Scores obtained by children under four whose precocity had been arrested before the age of eighteen months, and those of teenagers and adults whose precocity was a thing of the past, were scattered over approximately the same range as those of children tested while still physically precocious.† Further, the children with high IQs belonged to families in which intellectual brilliance was not at all unexpected.

A child of nine with an IQ of 132 is said to have a mental age of twelve, but he is not a replica of a child of twelve with an IQ of 100, whose mental age is also twelve. Their similar mental ages guarantee no identity save that they were competent in following the instructions and in answering the questions of which an intelligence test is composed. It does not even guarantee that they answered identically the same questions in each case.

† The scatter of IQ scores among 17 children with idiopathic sexual precocity resembled that for adrenocortical precocity.

Between two such children there are many differences, the signs of which vary among comparable pairs of children. Yet, for all the diversity of specific signs, their general import is the same. The chronologically older child has had more years in which to repeat experiences, reiterate various operations of mastery and become thoroughly familiar with information through usage, even if he has not greatly increased the scope of his knowledge and skills. Figuratively speaking, there is a patina to his mental age which the younger child does not have. On an intelligence test, lack of time for consolidation of knowledge and experience shows up in the brilliant younger child in a hit-and-miss scatter of successes and failures amongst difficult questions; the less bright older child has less scattering of successes amongst failures. The scattering effect showed up amongst our physically precocious children as a divergence between verbal and nonverbal scores in many instances, though there was no consistent tendency for the one or the other to be higher.

When a high IQ is combined with precocious physique and strength, a child has the appearance to pass socially as belonging in a higher age range, and he has as well the mental and physical resources to keep in step with older children. Yet he does not do so automatically but only by building up a repertoire of information and skills until they become second nature through repeated usage. Only practice makes perfect, and practice requires time, even though the special advantages of precocity may permit some short cuts. A precocious six-year-old may be powerful enough to play baseball with eight-year-olds, but the older lads have to teach him the rules of the game and to tolerate his beginner's poor coordination as pitcher and batter.

With three exceptions, all of the twenty-two children under consideration played sometimes, but not exclusively, with children bigger than their contemporaries. At other times, they joined in the activities of children their own age, with interests and enthusiasms incongruous with their size. In their everyday routines and activities, none of the twenty-two had so completely outstripped their contemporaries as to leave them trailing remotely in the rear. They were progressing through school at the usual rate, except in the case of three boys for whom a year's acceleration was arranged after endocrine and psychologic examination.

In interviewing these children, those between the ages of three and five especially, it was necessary, a high IQ notwithstanding, to be on the alert not to take for granted too great a repertoire of information and skills consolidated through repetition—which was perilously easy to do, in view of the mature appearance of the children. One searched constantly for the child's own familiar word or phrase, for examples familiar in his own life experience, and for demonstrations and operations to be carried out and made familiar in the here-and-now.

Even the parents of precocious children, those with high IQ as well as low,

had constantly to remind themselves of the chronological age of their child, and to lower their expectations of behavior and competence accordingly. Strangers easily made the mistaken conjecture that a precocious child was a nonprecocious one with some sort of psychological impairment: so far was overall psychological maturity divergent from bodily maturity.

As a child enlarges his repertoire of accomplishments and achievements and gains mastery in the face of more and more challenges, he also exercises, as a reciprocal of mastery, appropriate regulatory controls and disciplinary constraints. Control and constraint are inevitable ingredients of finesse and coordination of language, thought or movement, as well as of gross behavior and conduct.

Like mastery, control is refined and consolidated by way of practice, and it takes time. Physically precocious children, regardless of IQ, regularly show some signs of a time lack in the establishment of finesse and precision of control in the maneuvers of mastery for which their physical development has prepared them. The rough edges show up in a variety of manifestations which, being appropriate to chronological age, but not to stature and physique, produce an incongruous effect. A precocious child of three may have the limbs and strength of a six-year-old, but he employs them in an outbreak of rebellion like a child of his own age, and the effect resembles that of almost maniacal fury in an older youngster. Unrebellious, the same child is likely to be clumsy and heavy footed. The precocious infant boy may also have a deep-pitched adolescent voice, but he uses it with vocal inflection and intonation, word enunciation and sentence structure that bespeak infantile naivety. So too, a sexually precocious boy of eight may look like a veritable young man but, even though he abides by many of the constraints that constitute adolescent etiquette and propriety, he makes enough faux pas, and lapses often enough into the gaucheries of exuberant juvenile gesture and talk, to brand himself as a novice.

Reciprocal interplay between mastery and control in the overall behavior and conduct of our twenty-two hyperadrenocortical children was chronically lopsided, requiring that the patient be appraised as psychologically maladjustive, in only four instances. Two of these four were female pseudohermaphrodites, their shaky adjustment an accompaniment of their sexual ambiguity rather than their precocity. Another was also a female pseudohermaphrodite, one successfully treated so that she was an unvirilized, post-pubertal female by the age of twelve, around which time she did some compulsive stealing, notably of a wrist watch from the home of friends. Her symptomatic stealing appeared to be an accompaniment of adolescent sexual conflict centered round her handsome young stepfather. The fourth was a male whose conduct disorder was closely associated with the crippling after-effects of Perthes' disease, rather than with hyperadrenocortical precocity.

The other 18 of the 22 children were appraised as having adequate or good psychological adjustment, though two were extreme mental defectives, one congenital, one postconvulsive. All shared in common a vulnerability to teasing and thoughtless comment on account of their precocious size and appearance, but they all developed serviceable techniques for dealing with this stress, some of them unaided, some with the help of minimal psychological guidance.

Sexuality in hyperadrenocortical precocity is discussed in the paper that is companion to this one.

SUMMARY

Sixty infants, children and adults, representing seven types of hermaphroditism and including 39 hyperadrenocortical females, have been under comprehensive psychologic investigation. Gender role and outlook as boy or man, girl or woman, was found to be in agreement with sex of rearing, except in three cases, and not to be automatically or instinctively determined by chromosomes, gonads or hormones. Twelve hyperadrenocortical females and ten males were under study while still precociously virilizing. In psychological maturity, they resembled children of their age, though precocious physique, when combined with high IQ, permitted acceleration of psychological development in some respects, if life experiences also promoted it.

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HERMAPHRODITIC GENITAL APPEARANCE, REARING AND EROTICISM IN HYPERADRENOCORTICISM*

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Chromosomal, gonadal or hormonal determination of psychosexual orientation has, since the advent of modern techniques in chemistry, microscopy and other clinical sciences, been the viewpoint favored by the prevailing climate of medical opinion. In the companion paper of this pair, this viewpoint was examined by Money and the clinical evidence failed to support the assumption that the gender role of an individual is automatically determined by his gonads, hormones or chromosomes. On the contrary, the evidence indicated that a person's gender role and awareness is founded in what, from infancy onward, he learns, assimilates and interprets about his sexual status from parents, siblings, playmates and others, and from the way he reads the signs of his own body. In brief, a child grows into a gender role against the background of myriad experiences encountered and transacted.

It is possible for an hermaphroditic child to grow into a gender role contradictory of chromosomal, gonadal or hormonal sex. Perhaps even more remarkably, he or she may also grow into a gender role contradicted by predominant appearance of the external genital organs. Cases of contradiction between external genital appearance and assigned sex are extremely instructive. But they are rare, for when any infant is born, the signs from which those in attendance assign a sex to the infant are those of external genital appearance. In the case of an infant with hermaphroditic genital appearance there is usually a less automatic consideration given to external genitals. Nonetheless, genital appearance is an important factor. Of 60 hermaphroditic individuals studied, over half were assigned to the sex most appropriate for their genital appearance.

Among the 60, there were only 22 who, at the time they were studied, had lived for more than two thirds of their lives with a contradiction between external genital morphology and assigned sex, and of these, 15 older untreated females with hyperadrenocorticism formed the largest subgroup.

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TABLE 1

External Genital Appearance and Rearing Contradictory

22 Cases

Predominant Ext. Genital Appearance	Gonads	Endogenous Hormones	Assigned Sex and Rearing	Sexual Orientation	Type of Hermaphroditism
15 ♂	15 ♀	15 ♂	15 ♀	15 ♀	♀ hyperadrenocorticism
1 ♀	1 ♂	1 ♀	1 ♂	1 ♂	♂ cryptorchid hypospadiac with breasts
2 ♀ 2 ♂	2 ♂ 2 ♂	2 juv. 2 ♂	2 ♂ 2 ♀	2 ♂ 1 ?♂ 1 ♀	♂ cryptorchid hypospadiac
2 ♂	2 ♂	1 ♂ 1 juv.	2 ♀	2 ♀	♂ cryptorchid hypospadiac with mullerian organs

Evaluation of the pervasiveness of an individual's sexual orientation raises the age old problem of there being no standardized measuring rods or scales to employ. In our research, we have faced the problem as squarely as we can by giving due consideration to the following: general mannerisms, deportment and demeanor; play preferences and recreational interests; spontaneous topics of talk in unprompted conversation and casual comment; content of dreams, daydreams and fantasies; replies to oblique inquiries and projective tests; evidence of erotic practices; and finally the individual's own replies to direct inquiry.

Table I shows in very brief summary the findings concerning those individuals who, for one reason or another, did not receive surgical correction of their genital deformity in infancy and who lived with a contradictory genital appearance for at least 5 and as many as 47 years—that is, for more than two-thirds of their age at the time of study. The table illustrates, if nothing else, the surprising adaptability of the human organism. In all but one instance the person had succeeded in coming to terms with his, or her anomaly and had a sexual orientation wholly consistent with assigned sex and rearing. It is not to be contended that these people met with no difficulties in their lives. Feelings of bashfulness, shame and differentness and great difficulty in talking about themselves were found in some, but by no means all cases. In a very few instances, evidence of definite neurotic symptomatology was apparent. Psychotic symptoms were conspicuous by their absence.

Without delving too deeply into the significance of correlative facts and factors, one may interpret these findings to mean simply that most children can completely overcome the quandary of anomalous genital appearance and grow up with a sexual orientation appropriate to their assigned sex. Other children privately construe that an error has been made and can adapt themselves to

a psychosexual orientation appropriate to their assigned sex only at the penalty of one or another kind of neurotic symptomatology or, at best, with an uneasy kind of adjustment to life in general.

There are, of course, other factors which shape a child's gender role beside observed anatomical contradiction and the child's own private doubts about the correctness of his sexual identity. First is the effect of adult equivocation and doubt, particularly the concerns of the parents as to the correctness of their child's sexual identity and their concerns about the significance of the genital anomaly. One cannot tabulate degrees of parental equivocation, nor can one index parental misgivings and doubts. Without the benediction of chart or table, let it be stated that parental confusion or uncertainty was found to be a most potent factor in contributing to uncertainty or instability in the offspring.

Hardly less potent in its effect on the child was doubt and uncertainty on the part of medical advisors about the child's sexual status. More than once, a medical advisor discovered an incongruity between assigned and gonadal sex and, swayed by the conception that chromosomes, gonads, and hormones determine psychosexual maturation, felt it his duty to advise a change of sex in later childhood. We have talked with some few parents who, assured by their own thoroughgoing conviction of the boyness of their son or the girlness of their daughter, have been guided by their homely wisdom to ignore such a recommendation. Such medical pronouncement easily aroused great anxiety in parents and resurrected the ghosts of worry at the time of the child's birth, worry which had long since been fairly satisfactorily resolved in the light of day-to-day evidence that the child completely belonged in the sex assigned.

Whatever the ultimate decision, a child cannot avoid sensing any debate that goes on around him. Oddly, even in children old enough to have some opinion, in our experience it has been rare that they have been given any opportunity to express it. Historically a change of sex has been imposed more often than consented to.

The second factor contributing to a child's doubts as to his sexual identity has been his own uncertainty and ignorance, reinforced by curious questioning or teasing at the hands of his siblings or schoolmates. A fairly regular occurrence in the uninformed hermaphroditic child subjected to innuendo or teasing has been the development of a conviction that, although he thinks and feels like, say, a boy, physically he is half boy, half girl. One patient expressed it as "feeling like an 'it'." Both the children and their parents have gained a workable understanding of the anatomical problems, and have been reassured, when given elementary embryological information about normal sexual differentiation. Simple diagrams have been used to advantage. One embryological concept that we have found indispensable in bringing enlightenment to parents and children alike is this: that the child is, in fact, a girl or a boy who did not get finished, genitally, and is not a half boy, half girl.

While the most far-reaching implications of the studies we are making may

be the light our findings shed on certain basic psychiatric theories, they are also relevant to certain clinical decisions which arise in handling problems of hermaphroditism. Among the thorniest decisions which a doctor may face is the issue of change or reassignment of sex, with or without accompanying surgery. This issue is particularly thorny nowadays with regard to female hyperadrenocortical hermaphrodites not living as girls. Some of them were considered cryptorchid hypospadiac males at birth, assigned to the male sex and reared as boys until middle or late childhood when the correct diagnosis was made. Others, born in the precortisone era, were correctly diagnosed at birth but were reared as boys in order to spare them the psychologic turmoil of paradoxical

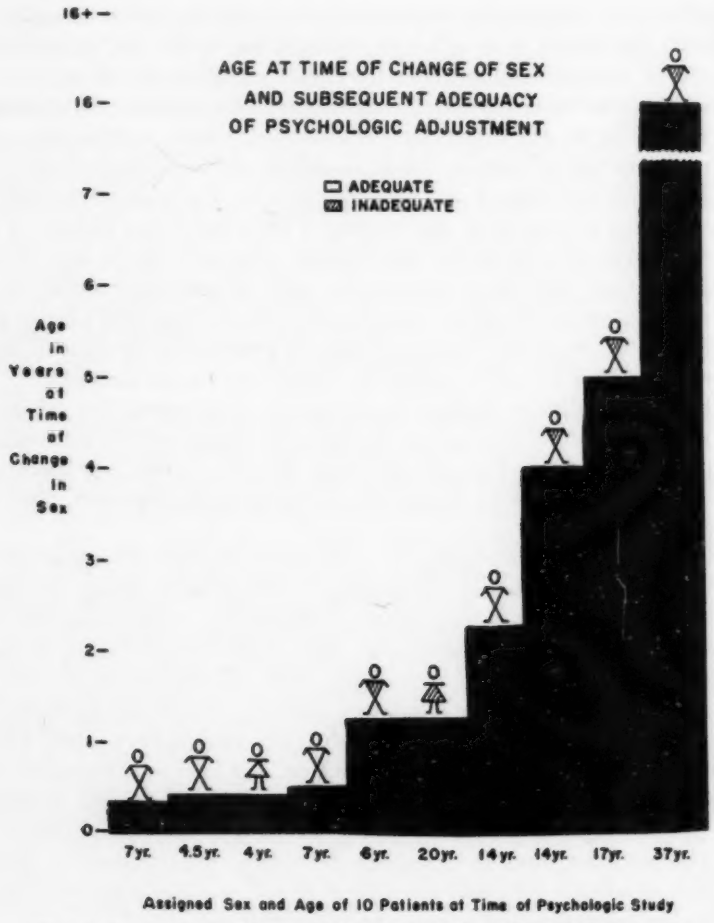

FIG. 1. Assigned sex and age of 10 patients at time of psychologic study.

excessive virilism. The problem is whether these boys, no longer infants-in-arms but schoolboys, should be feminized with cortisone and changed to live as girls.

We have studied 10 patients, not all of them with hyperadrenocorticism, who have undergone a change of sex after the neonatal period. They are listed in Figure 1. The figure includes only those patients studied at least 3½ years, and up to a maximum of 20 years after the sex change. In each instance an appraisal has been made with regard to pervasive thoroughness of sexual orientation in the sex assigned at the change, using the criteria of psychosexual orientation detailed on page 266. An appraisal was also made in each case of the successfulness and stability of day-to-day living adjustment, with deliberate intention, if any doubt existed, of erring on the side of over-scrupulousness, rather than allowing the benefit of the doubt.

The figure speaks for itself. The 4 who underwent a sex change before their first birthday had no subsequent disturbance psychologically. With one exception all 6 remaining were rated as inadequately adjusted. The exception was a boy who, in all fairness, had to be rated as adequately adaptive, since what problems he had were typical for many boys of his religious and moral upbringing, and likely to be transient.

A digression concerning an hermaphrodite's request for a change of sex seems necessary at this point. Our personal experience is small, but such evidence as is available suggests that the hermaphroditic individual who, at adolescence or later, asks for a change of sex, or takes matters into his own hands and makes a change, may not necessarily be making an impulsive request. For many years he may have been living with the quiet conviction that an error was made in infancy. In such instances our experience would lead us to give serious consideration to this type of request, provided external genital morphology gave even remote hope of adaptation to the new sex role. We would, however, have misgivings as to whether such an individual could ever gain more than a token identification with either sex.*

In Money's survey (1) of the literature of the last half century, he found reports of 26 hermaphrodites who in the teenage or later insisted on, or agreed to a change of sex; 25 wished to change from females to live as men. Only one of the 26 wished, or more accurately, agreed to renounce male status for womanhood. One may speculate as to the reason for this preponderance of changes towards male status. A consideration of the localization of sensations deriving from the genitals is relevant—a consideration somewhat tangential to the foregoing discussion of the appearance of the genitals. The older hyperadrenocortical female patient frequently has not only a well developed phallus, but in the untreated state, a phallus markably susceptible to erections, occasionally with

*Lest there be any chance of misinterpreting these remarks, let it be emphasized that this is not a discussion of requests for mutilatory surgery or hormonal treatment from anatomically normal people, homosexual transvestites, for instance, but only voluntary requests in older individuals with ambiguous genital appearance.

TABLE II

Reported Orgasm in Six Women Before and After Clitoral Surgery

Age at time of clitoridectomy	20	4	8	15	34	46
Age at time of study	30	22	14	26	35	49
Report of orgasm						
Before surgery	—	—	—	—	—	+
After surgery	—	+	+	+	+	+

priapism. The presence of such an organ can hardly fail to add to the quandary of the woman with regard to her sexual status, and may modify her sexual orientation. The adult untreated women with hyperadrenocorticism whom we have seen have been driven more often than not to frequent masturbation, sometimes with desperate urgency, despite personal taboos. One may conjecture that in these few women reported in the literature as desiring or aquiescing to change and live as males there were modifications of psychosexual orientation due to the constant sensory awareness of having a penile-like tumescence, especially if a normal vaginal opening were absent. In the patients we have talked to, the feminine role had become so thoroughly ingrained that not even a large erectile phallus had challenged the certainty of erotic role, though in each instance the woman spoke of her erectile phallus as having been the source of immense distress, morally if not physically.

When treatment of a girl with hyperadrenocorticism is undertaken, a decision must frequently be reached as to the need for, and advisability of plastic reconstructive genital surgery. To make normal-looking female external genitals, it is often conspicuously advisable to extirpate or amputate an enlarged phallus in addition to plastic remodeling of the urogenital sinus. Yet, many surgeons have hesitated to deprive a patient of what some authorities have declared the most significant erotic zone in the female.

On this issue, the findings of our studies promise to be useful in guiding clinical decisions. The effect of clitoridectomy on sexual responsiveness is one of the questions we are pondering currently. We do not feel we can answer all the questions at present, but some of the evidence gathered from our older patients is herewith cited.

Only six women were sexually experienced enough to have a full range of information to give (Table II). In evaluating sexual responsiveness we have not included states of sexual excitement short of orgasm, and have recorded as positive only those sensations vividly described as climactic in character. So far as it goes, the evidence demonstrates that clitoral amputation in childhood or later proved detrimental neither to subsequent erotic responsiveness, nor to capacity for orgasm. Information from two of the women was of special significance: one of them experienced orgasm for the first time after clitoridec-

tomy in her thirties, and another was very active sexually with ready accomplishment of orgasm 18 years after radical clitoral amputation when she was four years old.

In weighing the balance of factors in decisions about clitoridectomy, psychologic difficulties consequent on growing up with a large phallus should not be underestimated. The testimony of several of our patients has borne out poignantly the dilemma of such girls—they have been subject to personal doubts and misgivings and to teasing and questioning from others.

Our best estimate of the optimum time for clitoridectomy is that it should be as early as is consistent with surgical safety, even at the cost of postponement of vaginal reconstruction until a second operation later in life. The preschool age has proved undesirably late in some instances. An early operation serves additionally to remove parental doubt. Despite medical explanations of the femininity of their daughter, some parents have continued to have doubts —doubts nourished by their daily awareness of what they have construed as a male organ. When the clitoris is not strikingly hypertrophied, remaining fairly inconspicuous and almost concealed between the labia majora, there seems to be no need to do anything beyond giving the parents some explanation and guidance.

The considerations, in both this paper and in the companion paper by Money, of chromosomal, gonadal and hormonal sex, of external genital appearance and functioning, and of gender role and erotic orientation, all have pertinence to the problem of assigning a sex to a newborn hermaphrodite. Our recommendations are: in assigning a sex to a newborn hermaphrodite, regardless of the etiology of the condition, primary consideration should be given not to the chromosomes, gonads, or hormones, but to external genital morphology. If the external genitalia cannot possibly under any conceivable circumstance be surgically reconstructed for functioning in one sex, then the other sex should be assigned and subsequent medical and surgical efforts should be directed towards securing hormonal as well as morphological congruity with assigned sex. In cases where the external genitals of a neonate are sufficiently ambiguous to permit of serviceable reconstruction as either male or female, greater attention may be paid to hormonal sex should the case permit predictions about hormone functioning at puberty, due allowance being made for corrective hormonal intervention, as with cortisone.*

*These recommendations apply to all varieties of hermaphroditism, hyperadrenocorticism in females included. In the overwhelming majority of cases of the latter variety it is found that the external genitals are sufficiently ambiguous to permit easily of surgical feminization. Serious debate would arise only in the extremely rare case of an hyperadrenocortical female infant who had a normal looking penis with a fully formed urethra, and a normal looking empty scrotum. In such an instance surgical feminization is likely to prove difficult without complete extirpation of all areas of erotic sensation, and one may argue very seriously the advisability of feminizing procedures.

In decisions regarding change of sex in infant hermaphrodites up to about a year of age, the foregoing recommendations remain unchanged, except for one extra proviso, namely, the ability of the parents to negotiate a change of sex in their child. If given adequate explanation, the majority of parents have proved themselves able to take their infant's change of sex sensibly and in their stride. Those to whom we have talked recalled the period of change as an extremely disturbing experience, but changes made within the first year have proved thoroughly successful.

We are not able to give a fixed date-line before which a change of sex can be imposed with impunity and after which only with danger; there are too many differences between children and between the families and communities in which they live. Some children show beginning signs of awareness of their own gender by the age of 18 months, but far more important at this age is the parents' ingrained conviction that they have bringing up either a son or a daughter. It has proved extremely difficult for parents to relinquish a son for a daughter, or vice versa, after living with the child for a year or more. Admittedly the parents may be helped over this hurdle but only if they sever ties with casual friends and neighbors and re-establish their family in a new community. Without the move, the child is too likely to be harried and disturbed by rumor and gossip in later years.

By the age of 2½ years, when gender role is indelibly established, change of sex should in general be avoided. It may, however, sometimes be dictated by the anatomy of the genitals; regardless of all other male or female indices, the external genitals can sometimes be made functional surgically, only by reassignment of sex. At this age, under such circumstances, a change of sex might be seriously considered, but in full light of the knowledge that there will be, in some degree or other, ensuing problems of psychologic adjustment, and provision for extended psychiatric follow-up should be planned.

After the transition from infancy to childhood,—a transition which is not at the same age for all infants—children are virtually incapable of coping with a change of sex. Changes by medical or parental edict at this age are fraught with severe psychologic hazard for the child. Voluntary requests for change of sex in postadolescent hermaphrodites have been discussed earlier in the paper.

In conclusion, brief mention should be made of the hyperadrenocortical patients, girls and boys, numbering 22 in all, who have been studied during the period when physical precocity was manifest. For the 12 girls, the precocity was overshadowed in importance by the paradoxical virilization, but for the 10 boys, physical precocity was the predominant manifestation. In boys and girls both, however, the findings were in no way dissimilar to those of idiopathic sexual precocity (2, 3) which in briefest summary, may be stated as follows. In children manifesting physical precocity, psychosexual development

in each instance was appropriate for the chronological age of the individual and his life experiences rather than for physical size and somatic sexual development. Some few children recounted more persistent sexual imagery than their contemporaries, but the content of their fantasies did not include genital eroticism. Their erotic practices, if any, were chiefly masturbatory and similar to those of their contemporaries. The children showed themselves capable of establishing and maintaining serviceable standards of sexual restraint and conduct; they benefited from straightforward explanation of their condition and from information about appropriate behavior and conduct.

SUMMARY

External genital morphology agreed with assigned sex in over half of the 60 hermaphroditic individuals studied; it was therefore a salient determinant of the experiences they encountered from the day of birth onward and, subsequently, of the life experiences they transacted. Among the 22 who lived with a contradiction between external genital morphology and assigned sex, 21 had a gender role and erotic practices wholly consistent with assigned sex and rearing. Prompt and unequivocating decision of the sex of assignment was found beneficial, along with early reconstructive genital surgery, as required. Reassignment or change of sex in childhood, with or without genital surgery, was found to constitute an extreme psychologic hazard. Physically precocious children presented no untoward social problems of sexual misconduct.

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MAGNESIUM BALANCE IN MYXEDEMATOUS PATIENTS TREATED WITH TRIIODOTHYRONINE*

PRELIMINARY NOTE

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INTRODUCTION

Dietary deficiency of magnesium produces a syndrome characterized chiefly by vasodilatation, hyperirritability of the nervous system, cardiac arrhythmia, increase in the urinary excretion of calcium, as well as loss of weight and terminal fever (1–4). These changes are quite reminiscent of hyperthyroidism in man.

On the other hand, the major changes resulting from excessive magnesium administration are not unlike those found following removal of the thyroid. Magnesium produces a depression of both the central nervous system and the neuromuscular junction (5). The sympathetico-adrenal system is sensitized both by magnesium deficiency and the administration of thyroxine (6); the excitability of the system is lowered following thyroidectomy and restored by a magnesium-deficient diet.

Changes in the serum levels of magnesium in hypothyrodism and hyperthyroidism are not especially striking or revealing, since the observation that the percentage of diffusible magnesium in the serum is decreased in thyrotoxicosis and increased in myxedema has been disputed (cf. 7, 8). It is of some interest, however, that parenteral administration of magnesium to hyperthyroid patients by Hueber (9) resulted in clinical improvement. Basal metabolic rates were reduced from plus 24–60 to plus 7–13 in three days. Dine and Lavietes (7) state that they failed to confirm these findings without presenting details.

The present investigation was undertaken to examine further the possibility of a relationship between the thyroid hormone and magnesium. Metabolic studies which had been carried out on the wards of The Johns Hopkins Hospital by Dr. S. P. Asper, Jr. provided the opportunity to investigate one aspect of this possible relationship, namely, the magnesium balance in myxedematous patients before and after treatment with L-triiodothyronine.

METHODS

These balance studies were conducted on the Metabolic Ward of The Johns Hopkins Hospital under the supervision of Dr. S. P. Asper, Jr. Two patients with classic myxedema were placed on a constant diet designed to maintain approximate nitrogen equilibrium in

* This work was supported by grants from the Nutrition Foundation, Inc., U.S. Public Health Service, and conducted while on a Life Insurance Medical Research Foundation Post-doctoral Fellowship.

normal subjects (10). Complete details of the balance study are presented in the preceding paper (11).

Urine was collected in 24-hour periods ending at 9:00 a.m. daily with alcoholic thymol and acetic acid added as preservative and acidifying agents. Diets and pooled stool specimens were processed as described by Howard *et al.* (10). The specimens were provided through the kindness of Dr. S. P. Asper, Jr., and had been stored (urines refrigerated) for four to six months prior to analysis.

Urinary magnesium was determined by precipitation of ammonium magnesium phosphate following removal of calcium (12, 13). The precipitate was recovered from a fritted glass filter and the phosphate determined according to Gomori (14). Diet and stool specimens were prepared by wet ashing (15), and magnesium determined as above. Citrate was added to prevent the precipitation of an iron complex with the magnesium ammonium phosphate.

Oxygen consumption (basal metabolic rate) was estimated by means of a commercial respiratory calorimeter. Determinations were performed in duplicate at 8:00 a.m. daily. Each patient received subcutaneously 1 mgm. of D-triiodothyronine on day 4, the racemic mixture on day 10, and the L-isomer on day 19.

Results

The clinical response following the administration of triiodothyronine, as well as changes in serum constituents, and the balance of nitrogen, creatine,

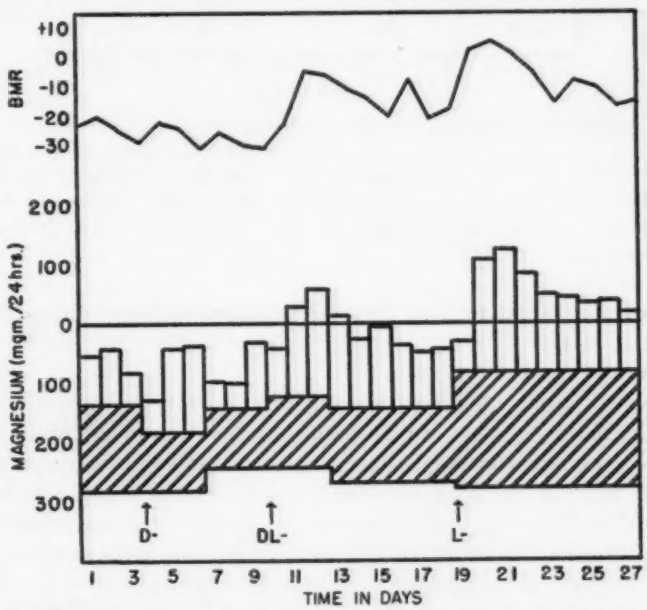

Fig. 1. Magnesium balance in patient B.R. following subcutaneous injection of 1 mgm. of D-, DL-, and L-triiodothyronine on days 4, 10 and 19 respectively. Dietary magnesium (milligrams) is represented by the distance below the zero line; fecal magnesium is denoted by the diagonal lines; and urinary magnesium by the open bars. Magnesium balance is represented by the distance from the top of the bar to the zero line. Daily determinations of oxygen consumption (BMR) are presented at the top of the figure.

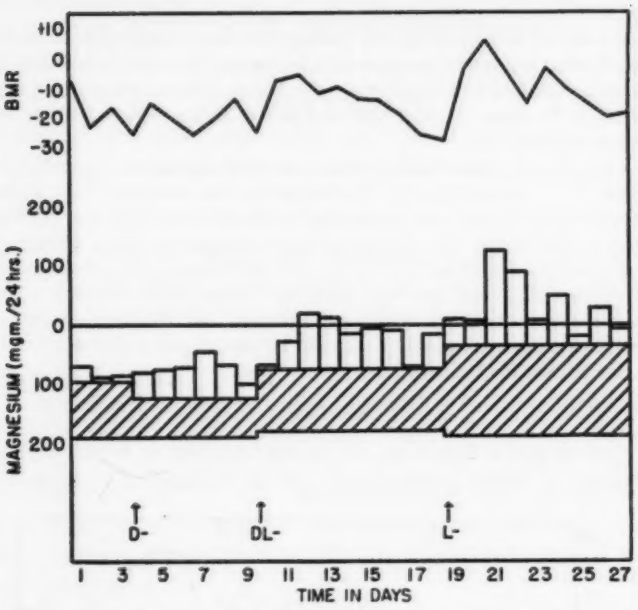

FIG. 2. Magnesium balance in patient R.S. following subcutaneous injection of 1 mgm. of D-, DL-, and L-triiodothyronine on days 4, 10, and 19 respectively. Dietary magnesium (milligrams) is represented by the distance below the zero line; fecal magnesium is denoted by the diagonal lines; and urinary magnesium by the open bars. Magnesium balance is represented by the distance from the top of the bar to the zero line. Daily determinations of oxygen consumption (BMR) are presented at the top of the figure.

creatinine, and phosphorus, will be published in another communication (11). In both patients the D-isomer produced little or no effect, and the L-isomer a marked response.

The changes in magnesium balance are presented in Figures 1 and 2. Positive magnesium balance existed in both patients before treatment. An increase in the urinary excretion of magnesium was produced approximately 24 hours following injection, reaching with the L-isomer as much as three times the control values. The increase in magnesium excretion with the D-isomer was equivocal, and in neither patient sufficient to give a negative balance. However, a negative balance was produced in both individuals when the L-isomer was given alone or in the racemic mixture. Following L-triiodothyronine administration, urinary excretion of magnesium approached the dietary intake in both patients. There was no correlation between magnesium excretion and urine volume.

Changes in fecal excretion of magnesium appear to be a reflection largely of

variation in the volume of stool. The quantity of magnesium per gram (dry weight) of stool remained relatively constant throughout the balance period. The total magnesium balance was positive in both patients during the control period. The net magnesium loss following the injection of 1 mgm. of L-triiodothyronine represented three to four times the presumed total quantity of magnesium in the serum.

Discussion

These observations offer no information to indicate whether the diuresis of magnesium produced by administration of L-triiodothyronine to myxedematous patients is a primary effect of the thyroid hormone, or an effect secondary to the increased metabolism. Furthermore, it may not be concluded from this study that a negative magnesium balance necessarily occurs in hyperthyroidism. In fact, Tibbetts and Aub (16) have reported that two patients with hyperthyroidism were in positive magnesium balance. On the other hand, post-prandial urinary excretion of magnesium was found to increase in thyrotoxicosis (7).

It has been found that thyroxine can uncouple oxidative phosphorylation in mitochondria *in vitro* (17, 18); this effect has been suggested as the physiological action of thyroid hormone (17). This uncoupling is reversed by Mg^{++} (19), an effect which is probably occasioned by the great insolubility of the magnesium-thyroxine complex (20). It appears premature to suggest that this antagonism is the specific point of physiological interaction of thyroid hormone and magnesium. However, in view of the known importance of magnesium ions in many enzymatic reactions, particularly transphosphorylations, it is quite conceivable that thyroid hormone may affect the intracellular site or function of critically placed magnesium ions, one result of which might be changes in magnesium excretion such as those observed in this study.

It is appreciated that the similarity between magnesium deficiency and thyrotoxicosis, and between myxedema and the known effects of magnesium excess remarked on in this paper may be no more than coincidence. However, recognition of these similarities may lead to new and significant information on the mode of action of the thyroid hormone.

Summary

1. A negative magnesium balance was produced in two myxedematous patients by the administration of L-triiodothyronine.

2. The similarity between thyrotoxicosis and magnesium deficiency, as well as between myxedema and the known effects of magnesium excess, is emphasized.

Acknowledgments

This investigation was conducted in the laboratory of Dr. A. L. Lehninger, with his constant encouragement and advice. The author is indebted to Dr. S. P. Asper, Jr. and Dr.

A. M. Harvey of the Department of Medicine, The Johns Hopkins Hospital, for their generous cooperation.

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ABSTRACTS OF PAPERS PRESENTED BEFORE THE JOHNS HOPKINS MEDICAL SOCIETY

March 14, 1955

STUDIES ON THE PATHOGENESIS OF FEVER

IVAN L. BENNETT, JR.

The hypothesis most commonly offered to explain the disturbance of body temperature by diseases of various types states that fever is the result of the action of products of tissue injury upon the cerebral centers controlling body temperature. Most previous attempts to demonstrate fever-producing substances in injured tissues are open to question because of failure to take precautions to avoid contamination by the pyrogenic products of bacteria. The present studies have been carried out under conditions that avoided pyrogen contamination. An extensive survey of extracts and suspensions of normal rabbit tissues, tested by intravenous injection in normal rabbits revealed the presence of a heat-labile fever-producing substance in extracts of polymorphonuclear leukocytes. The properties of this substance differ substantially from those of bacterial pyrogens or previously described tissue pyrogens. Recently completed experiments have shown that a similar substance appears at the inflammatory site and in thoracic duct lymph of rabbits with pneumococcal peritonitis. Furthermore, the appearance of this substance coincides with the onset of the fever of this infection. Its presence in lymph, of course, indicates its access to the venous circulation. Finally, if fever in the host subsides after penicillin treatment of the pneumococcal infection, this substance is no longer demonstrable in exudate or lymph. Although it remains to be shown that this heat-labile pyrogenic material is truly a product of injured host cells, its properties are similar enough to leukocyte extracts to suggest such a source.

THE EFFECT OF CORTISONE ON INITIAL ATTACKS OF RHEUMATIC CARDITIS

MILTON MARKOWITZ

The results of cortisone therapy in 45 children, ranging in age from 4 to 14 years, with initial attacks of rheumatic carditis is presented. Group I consisted of 15 children who were treated on a fixed dosage schedule of 4 grams of cortisone for a six week period. Only 6 of these 15 children had normal hearts after a minimum of six month post-therapy follow up. Group II consisted of 30 children who received 8 grams of cortisone for the first 6 weeks, and were then placed on a small daily maintenance dose for from one to ten months. The length of treatment varied with the course of the disease in each patient. Six months after treatment, 20 of the 30 patients in Group II had normal hearts. Twenty-two of these 30 patients were treated within 3 weeks of their onset, and 19 had no evidence of heart disease after treatment. On the other hand, of the 8 patients treated later in the course of their illness, 7 were left with rheumatic heart disease.

These results suggest that large doses of cortisone, and prolonged treatment may diminish or prevent heart disease if treatment is begun early. However, final conclusions on the value of cortisone must await further controlled studies on a large series of cases treated in this manner.

The side effects noted during cortisone therapy are presented. This form of treatment is not without hazard, and the physician must be alert to the complications, such as hypertension, masked infection, peptic ulcer, and psychosis.

HERMAPHRODITISM: CLASSIFICATION, DIAGNOSIS AND TREATMENT

LAWSON WILKINS

Sex differentiation involves successively the development of the gonads, the genital ducts and the external genitalia. The type of gonad is determined by the chromosomal pattern.

Experiments of Jost and others on early embryonic castration, show that in the absence of fetal testes the genital ducts and external genitalia always differentiate along female patterns. Development of the Wolffian and disappearance of the Mullerian ducts depend upon adequate secretions of fetal testes. These findings shed light on the abnormalities found in patients with various types of ambisexual development and gonadal dysgenesis.

Ambisexual development in humans can be classified as

A. Gonadal dysgenesis
B. Intersexuality
    1. true hermaphroditism
    2. male pseudohermaphroditism
    3. female pseudohermaphroditism without adrenal disorder
C. Female pseudohermaphroditism due to virilizing adrenal hyperplasia.

Patients with the so-called "syndrome of ovarian agenesis and stunted growth", who have absent gonads, have entirely female genital tracts and external genitalia but often have a male chromosomal pattern. A number of patients with this syndrome who have phallic enlargement have been shown to have mesonephric elements consisting of large nests of Leydig cells and rete tubules in the broad ligament.

In true hermaphrodites who have a testis on one side and an ovary on the other, the differentiation of the genital duct on each side conforms to the sex of the gonad. With combinations of ovotestes various types of development of the ducts and external genitalia are encountered.

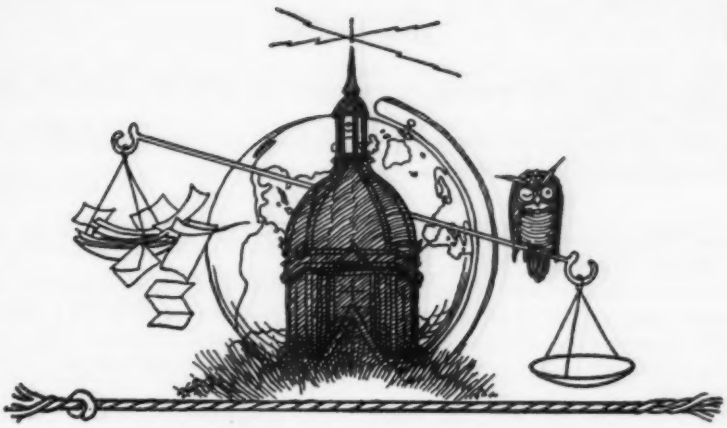
In male pseudohermaphrodites the external genitalia may simulate the male, be ambiguous or have entirely female configuration. Patients with female type of genitalia regularly feminize at puberty whereas others may either masculinize or feminize.

Female pseudohermaphrodites without virilizing adrenal hyperplasia are exceedingly rare. Several cases have been due to arrhenoblastoma in the pregnant mother. These patients are often mistaken for hypospadic males but they feminize, menstruate and ovulate at puberty.

About half of all cases of ambisexual development are due to congenital virilizing hyperplasia of the adrenals in females. It is most important to differentiate this type of hermaphroditism from all other types not due to adrenal disorders. This differentiation can be made in early infancy only by the demonstration of increased 17-ketosteroid and pregnanetriol excretion and other signs of excessive androgen secretion.

The sex of rearing should be decided as soon after birth as possible on the basis of careful diagnostic studies. Females with congenital adrenal hyperplasia should always be raised as girls. With proper cortisone therapy, virilization can be prevented and normal female development assured. In intersexes without adrenal hyperplasia, the sex of rearing should be selected largely according to the anatomy of the external genitalia. Male pseudohermaphrodites or true hermaphrodites who do not have adequate development of the phallus should be raised as females. Those who have entirely female external genitalia always feminize in spite of the presence of testes. In other male pseudohermaphrodites who are to be raised as females, orchidectomy may be advisable to prevent masculinization.

The sex of rearing rather than the chromosomal pattern or the type of gonads determines the psychosexual orientation and development of an individual. When a child has been regarded and raised steadfastly in a particular gender, psychologic confusion and abnormal sexual behavior do not occur. Change of the sex of rearing after the age of 2 or 3 years is psychologically hazardous and should be avoided. In some hermaphrodites it is advisable to resort to gonadectomy, the administration of sex hormones and plastic operations to make them conform as nearly as possible to the sex in which they have been reared.



BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of the Bulletin)

Human Physiology, 2nd edition. By BERNARDO A. HOUSSAY AND ASSOCIATES. Translated by Juan T. Lewis and Olive Thomas Lewis. 1177 pp., $12.00. McGraw-Hill Book Co. New York, N. Y.

This textbook, written by a group of Argentinan physiologists, under the leadership of Professor Bernardo A. Houssay is the second English edition of a version originally composed in Spanish. It is an exceedingly readable book possessing a clarity of presentation which is much to the credit of the authors and especially to one of them, Juan T. Lewis, who, aided by Olive T. Lewis, did the translation. Several chapters have been entirely rewritten since the first edition and new material has been added to others.

The book is divided into nine sections. The longest one, devoted to the Nervous System, occupies about 32 per cent of the book. Sections on Blood, Respiration, Internal Secretions, and Reproduction each take up about 7 per cent, Digestion 5 per cent, Circulation 14 per cent, Metabolism 16 per cent, and Urine Formation and Excretion 4 per cent. Each section is subdivided into a number of relatively short chapters (12 pages in length on the average), a feature which this reader finds conducive to perusal. The typography is excellent. A double column format is used. The illustrations, 504 in number, are clear and generally well labelled.

A well chosen bibliography of classical and general references is given at the end of each chapter. In addition, more specific references are given as numbered footnotes on the appropriate pages. An annoyance is the practice of placing a name parenthetically following a statement but all too frequently with no inclusion of references to this name in either footnotes or bibliography. Although in many, but not all, cases these names are well known to physiologists, they will not be generally familiar to beginning medical students.

The advanced physiologist can, of course, find things to criticize about the chapters dealing with his particular area of specialization but such complaints will probably be directed more to omission of material that might have been included rather than to errors of fact. In this connection it should be kept in mind that the book was written primarily to introduce medical students to the subject of Human Physiology rather than to serve as a reference book for professional physiologists. As the senior author states in the Introduction, "It is

far better to have precise knowledge of fundamental principles than vague ideas about a great number of facts".

I think that students who choose this text will find it a pleasant and informative introduction to the subject of Physiology.

ARTHUR B. OTIS

Vaginal Hysterectomy. (American Lecture Series). By LAMAN A. GRAY. 137 pp., $4.75. Charles C Thomas, Springfield, Illinois.

This short volume of some 120 pages is a most complete and informative study on a single operative procedure that is gaining ever widening support and popularity. It is not simply because the author is an erstwhile Hopkins resident and personal friend that evokes such an enthusiastic review, because any reader will immediately find that the book can stand easily on its merits.

The introduction does more than simply live up to its name but includes a fascinating history of the evolution of vaginal hysterectomy. Of interest is the fact that two of the most common earlier indications for the operation were carcinoma and (surprisingly) inflammatory disease, both of which diseases are currently felt to negate this type of surgery. The author then proceeds to discuss the indications for and advantages of the vaginal route to hysterectomy, at the same time stresssing the need for a trained gynecologist to be just as proficient in the abdominal procedure. He wisely deprecates a tendency for some enthusiasts to insist on the pelvic approach despite a large, fixed, uterus or other usually accepted contraindications.

Pre- and post-operative care receive appropriate coverage, but the 35 page section on operative technique is alone worth the price of the book ($4.75). The concise and accurate description is enhanced by a series of excellent diagrams that immensely facilitate comprehension and clarity. The operative technique is basically that of Heaney with certain modifications just as any experienced gynecologist will add little improvisations here and there according to preference and the dictates of an individual patient. There are some operators who might express surprise that the utero-sacral ligaments are not plicated to prevent or cure enterocele, but the author expresses his views on this procedure in the following chapter.

Any surgeon who denies complications is either a prevaricator or an infrequent operator. The final chapter is devoted to recognition and management of the common and uncommon complications that can happen to the unskilled or skilled vaginal surgeon. This is handled with the precision and clarity that is the keynote of this whole little volume. In the preface Dr. Gray states that his book is for the occasional vaginal operator but any skilled gynecologist, whether he lives in Baltimore, Chicago, or San Francisco, can profit by possession of this text.

EDMUND R. NOVAK

A Symposium on Amino Acid Metabolism. Sponsored by The McCollum-Pratt Institute of The Johns Hopkins University. Edited by WILLIAM D. MCELROY AND H. BENTLEY GLASS. 1048 pp. $12.50. The Johns Hopkins Press, Baltimore, Md.

This volume, the fifth to be published reporting a symposium of the McCollum-Pratt Institute, is a collection of papers presented and discussion engendered at meetings held at The Johns Hopkins University on June 14–17, 1954. As such, it summarizes the recent background of our current knowledge of amino acid metabolism and affords an intimate picture of the directions present researchers are taking, in the words of an impressive number of the acknowledged leaders in this field.

The book is divided into six main sections. The first contains a general consideration of

amino acid metabolism, while the other five deal with the metabolism of groups of related individual amino acids. Each of the 58 papers is supplemented with a list of references. Twelve sections, including about 70 pages, of verbatim discussion appear after the papers which they followed at the meetings. An 82 page summary by Dr. Bentley Glass concludes the volume. Author and subject indices are supplied, along with a list of participants in the discussions.

Many of the papers are exceedingly readable, and the longer contributions contain sufficient background information to orient the reader seeking to broaden his understanding of his field. Many previously unpublished data are encountered throughout the book, lending the volume somewhat the flavor of current journal literature.

As with any work of this sort which outlines the frontier of a very broad and fast-moving area of research, it is inevitable that much of the material will be quickly out-dated. However, the speculative elements are for the most part clearly recognizable and will perhaps always be of some interest from an historical viewpoint. The discussions are generally quite informal, often introducing unpublished information, and should make stimulating reading for anyone intimately concerned with the subjects treated.

MARY A. HILTON

Kritik der Psychosomatik. By HANS JÖRG WEITBRECHT with a foreword by Kurt Schneider. 114 pp., kartoniert DM 12 ($2.85). Georg Thieme Verlag, Stuttgart, Germany. Also Intercontinental Medical Book Corp., New York, N. Y.

The author concerns himself with various concepts of psychosomatic medicine such as what it is, the relationship of neurosis to disease, psychogenesis, symbolism, "endogeny" as applied to psychosomatic medicine and the general relationship of physician and patient. He quotes the work of such American authors as Alexander and Dunbar and among German investigators Von Weizsaecker finds frequent mention. Reference is made to the fact that psychoanalysts seem to have usurped the field of psychosomatic medicine and he rejects their attempt to establish a medical anthropology based on the psychoanalytic concept of neurosis. The author finds little evidence to support the theory of psychogenesis of illness and is cautious in accepting personality types or specific conflicts as being the basis of certain diseases. Freudian psychoanalysis has undergone so many changes in recent years, according to the author, that one may raise the question whether it constitutes a well-circumscribed depth psychology and how closely allied to psychosomatic medicine it actually is.

The monograph is well documented but obviously more a criticism than a critique. The author shows special interest in taking issue with psychoanalysis and calls for a return to principles of clinical psychopathology. His work points out that psychosomatic medicine is not a new discipline and that many notions about it are based on speculation rather than scientific fact. He offers no ideas of his own on the subject other than certain philosophical consideration on the concept of disease.

The monograph will bring some comfort to those readers of psychosomatic literature who find it difficult to attribute disease to certain stereotyped notions of orthodox psychoanalysis.

EDUARD ASCHER

Serological Approaches to Studies of Protein Structure and Metabolism. Edited by WILLIAM H. COLE. 97 pp., $2.00. Rutgers University Press, New Brunswick, N. J.

This volume contains six papers presented at the 10th Annual Conference on Protein Metabolism held on January 29th and 30th, 1954, under the sponsorship of the Bureau of Biological Research at Rutgers University. The first paper entitled "Proteins as Antigens

and Antibodies" and presented by F. Haurowitz is concerned principally with the nature of antigens and their fate following injection into a foreign host. This is followed by a consideration of the site and mode of antibody synthesis and some implications pertinent to the general problem of protein synthesis. The second paper delivered by M. Heidelberger and entitled "The Precipitin Reaction and the Studies of Native and Denatured Proteins and Derivatives" presents a brief review of the development and essential characteristics of the precipitin reaction, as well as certain applications to problems requiring study by the quantitative absolute method developed largely by Heidelberger and Kendall. This is followed by a paper by D. Gitlin on "Light Scattering and Ultracentrifugation Methods in Studies of Precipitin Systems and their Application to Human Metabolism". This paper is chiefly of interest because of certain problems in biology and medicine studied by the quantitative absolute precipitin method. The fourth paper by Melvin Cohn on "The Immunological Analysis of the Biosynthesis of a Protein" should be of interest to students of enzymology and microbiology since Dr. Cohn presents a detailed discussion of his studies on the mechanism of synthesis of β-galactosidase by *E. coli*. This is followed by an informative review on "The Use and Limitations of Serum-Agar Technics in Studies of Proteins" by J. Munoz. The final contribution to the Symposium is a paper by Alan Boyden on "The Measurement and Significance of Serological Correspondence Among Proteins". In this paper Dr. Boyden discusses the field of comparative serology as explored by a photoelectric technic of measurement, in contrast to the crude, essentially qualitative observations of older investigators. While the photronreflectometer which Dr. Boyden employs represents a useful tool for certain comparative studies, there are serious limitations which are not adequately discussed. These arise chiefly from the fact that the turbidity developed in a precipitin reaction depends not only on the quantities of antibody and antigen, but other factors as well. Some of these cannot be controlled adequately and thus present interpretational difficulties. Therefore, the significance of photronreflectometer readings is at best only relative, rather than absolute, in contrast to the technic described by Heidelberger and by Gitlin, in which the absolute quantity of specifically precipitably antigen-antibody compound is measured.

Considered as a whole, this collection of papers should make interesting and informative reading, not only for immunologists but also for many students of biology and medicine.

MANFRED M. MAYER

Shock and Circulatory Homeostasis. Transactions of the Second Conference, October 19, 20 and 21, 1952. Edited by HAROLD D. GREEN. 275 pp., $3.75. The Josiah Macy, Jr. Foundation, New York, N. Y.

This book contains the edited verbatim transactions of a three day conference on Shock and Homeostasis. The participants in the conference are all distinguished scientists and leaders in their respective fields, whose common interests are the physiological and biochemical alterations encountered in the study of shock. The conference concerns itself with two main topics. The first discussion is on the subject of the metabolic aspects of hemorrhagic and traumatic shock, led by Dr. Frank L. Engel of the Department of Medicine and Physiology at the Duke Medical School. The second and shorter portion of the volume discusses the distribution and possible physiologic functions of epinephrine and norepinephrine. The moderator of this seminar is Dr. U. S. von Euler of the Karollinske Institut, Stockholm, Sweden. Dr. Engel directs his portion of the conference into a broad discussion of changes in protein and carbohydrate metabolism in normal and adrenalectomized animals subjected to various forms of shock. The effects of shock upon hepatic blood flow and the effects of reduced blood flow upon hepatic function are considered at length. The effects of such drugs as Dibenamine and Dibenzyline are subjected to close scrutiny. Finally the relation of bacterial action to the development of the state of irreversibility in shock is debated. Dr. von

Euler reports the results of experiments on the distribution of norepinephrine and epinephrine in many animals, including man, and a prolonged debate ensues on the action of these substances.

Dr. Frank Fremont-Smith, medical director of the Josiah Macy, Jr. Foundation, states in his introduction that the basic purpose of the conference was to bring together the participants to exchange ideas, experience, data, and methods, and to promote "meaningful communication between scientific disciplines". From the point of view of this reviewer these aims are achieved in this Second Conference. As a book to possess, however, its chief value lies in the excellent review of previously published experimental work it affords. Excellent bibliographies are appended to which the only moderately informed reader must refer to appreciate fully the many fine points raised in the prolonged discussions. It is a book which will be of extreme interest to future research workers in these fields, but it has little place in the libraries of medical students or practitioners.

ALAN C. WOODS, JR.

Lehrbuch und Atlas der Anatomie des Menschen, Rauber-Kopsch, 19th edition, in 2 volumes, 1955. By FR. KOPSCH. Volume I: Allgemeines, Skeletsystem, Muskelsystem, Gefässsystem. 736 pp., Ganzleinen DM 64.50 ($15.35). Georg Thieme Verlag, Stuttgart, Germany.

This sturdy treatise is well known to professional anatomists, who will welcome this new edition by Professor Kopsch. As in the past, it is a combined atlas and text, a format which unquestionably has its advantages. The volume is abundantly illustrated, and more than a third of the figures are in color. The old, familiar illustrations have been reproduced, but for this edition new engravings have been used throughout, with good effect. The accompanying text shows the scholarly competence which the reviewer has come to associate with this work, which is well printed, on paper of excellent quality, and represents a good job of bookmaking. Volume 2 (Eingeweidelehre, Nervensystem, Sinnesorgane, Haut) is scheduled for publication in the near future.

A. L. G.

Primary Anatomy, 3rd edition, 1955. By H. A. CATES AND J. V. BASMAJIAN. 339 pp., $5.75. The Williams & Wilkins Co., Baltimore, Md.

The first (1948) and second (1951) editions of this text were issued under the sole authorship of Professor Cates. Now, after his death, this third edition has been prepared by his colleague, Dr. Basmajian, who has made many changes and corrections, and has introduced a considerable number of new drawings. From the beginning, and in this edition "more than ever, the material has been directed at students in Physiotherapy, Occupational Therapy, Physical and Health Education, Nursing, and similar collegiate courses in Human Anatomy." For such the book has found, and in this improved edition should continue to find, a rather wide area of usefulness. It is well printed, in readily legible type, on non-reflecting paper.

A. L. G.

Coronary Heart Disease in Young Adults: A Multidisciplinary Study. By MENARD M. GERTLER, AND PAUL D. WHITE, with the aid, advice, and editorial assistance of E. F. BLAND, J. FERTIG, S. M. GARN, J. LERMAN, S. A. LEVINE, H. B. SPRAGUE, AND N. C. TURNER. 218 pp., $5.00. Published for the Commonwealth Fund by Harvard University Press, Cambridge, Mass.

This monograph is a very important addition to a rapidly expanding knowledge of this vital subject. The studies described in it were conducted at the Massachusetts General Hospital upon groups of young patients who had myocardial infarction and suitable controls.

The multidisciplinary investigation sought clinical, genetic, biochemical, anthropological, and hormonal differences between the two groups to permit earlier detection, than is currently possible, of the individual likely to develop a myocardial infarct. The great preponderance of males over females in a group of patients with coronary heart disease was forcefully reemphasised. There were no noteworthy clinical differences. The familial incidence of the condition was found to be significant as was a particular type of body build.

The serum cholesterol and uric acid values were higher in the coronary group than in the controls and important interrelationships of the serum lipids were noted.

The book portrays forcefully the results of a study of extraordinary eminence. It points clearly to many fruitful additional approaches to further clarification of coronary heart disease. It does not indicate whether or not myocardial infarction is imminent in the individual patient except on a probability basis.

B. M. B.

Current Therapy—1954: Edited by HOWARD F. CONN. Latest Approved Methods of Treatment for The Practising Physician. 898 pp., indexed. $11.00. W. B. Saunders Co., Philadelphia, Pa.

This book, the 1954 addition to an annual series begun in 1949, maintains the high standards set by predecessors. It has been brought thoroughly up to date.

For those not familiar with the plan of previous editions the book provides a ready source of information on practical therapy for busy students and practitioners. A very wide selection of subjects is covered in the unusual manner of having two authorities present their views separately. There is no pretense that the discussions of therapy are exhaustive and they are not. In general, controversial views are avoided in order to focus attention upon practical measures of established value.

B. M. B.

A Textbook of Physiology, 17th edition. Edited by JOHN F. FULTON. 1275 pp., $13.50. W. B. Saunders Co., Philadelphia, Pa.

This book is the seventeenth edition of the text originally written by Dr. William H. Howell, long a physiologist at Johns Hopkins University, and the third edition published under the guidance of Dr. Fulton. The present edition, published six years after the last, is composed of the contributions of thirty specialists in various fields of physiology, seven of whom have not appeared as authors in the work previously.

Besides those authorities who wrote for this as well as the previous edition, Rosemary Biggs of Oxford now covers the subject of the coagulation of blood; William Blake of Oregon discusses body fluids and kidney function; Carlyle Breckenridge of Baylor University College of Medicine has collaborated with H. E. Hoff in a well rounded treatment of respiratory physiology; Thomas Forbes of Yale University School of Medicine now is the author of the section on the physiology of reproduction; Hernández-Peón of the University of Mexico discusses the physiology of body fluids; David Nachmansohn of Columbia University handles a new chapter on "Acetylcholine and Energy Transformation in Nerve Cells"; John L. Patterson of the Medical College of Virginia has helped with the discussion of the circulation through the brain, and Helen Wright of the University of London deals with general properties of blood. The contributions of all these authors, new to the present edition, appear entirely adequate.

Though the preface to the first edition, written by Dr. Howell, has been retained, Dr. Fulton's historical résumé of American physiology has for some reason been deleted.

David P. C. Lloyd has completely rewritten his section on the "Principles of Nervous

Activity", with reorganization and inclusion of much extraordinarily recent new material. However, the reviewer feels that Lloyd has somewhat casually treated the evidence for and the important implications of the hypothesis of saltatory conduction. Similarly, the recent work on the importance of the sodium ion in nerve conduction could have been dealt with more intensively than it has been.

The section by Dr. Fulton on the motor functions of the central nervous system has been slightly shortened but nevertheless now includes a new chapter on the limbic system which did not appear in the last edition. This is very much up to date. It might be mentioned casuistically in passing that the unfortunate term "autonomic afferents" instead of "visceral afferents" has slipped into this section.

The chapter on the peripheral division of the autonomic nervous system has been revised by E. C. Hoff.

This reviewer was particularly impressed with the range of Nahum's chapter on "Electrical Correlates of the Cardiac Cycle", and also does not believe that he has ever seen a better treatment of the neurogenesis and regulation of respiration than that by Hoff and Breckenridge in their chapters on these subjects. Also to be commended is the mention of various types of evoked cortical potentials.

The question arises with a book of this size as to whether information on energy transformations in muscle and on the histology and physical chemistry of blood really belong in a textbook of physiology and should not be treated separately in the disciplines of biochemistry and histology. Omission of this material from the present volume would probably have resulted in a more compact treatment of information which more properly and unquestionably belongs to the domain of physiology.

One can also not help having reservations as to whether such an exhaustive, detailed and well documented treatise as this is the most useful kind of a textbook for first-year medical students. It would probably be impossible in a first-year physiology course for a student to be able adequately to digest all the material in such a book as Fulton's Physiology. However, for those of us with more leisure the new edition should be useful, since it continues the tradition of this text containing some of the most outstanding treatments of the various aspects of physiology available.

PAUL O. CHATFIELD

BOOK RECEIVED FOR REVIEW

Advanced Surgery of Cataract. By DANIEL B. KIRBY. 271 pp., $27.00. J. B. Lippincott Co., Philadelphia, Pa.

Antisera, Toxoids, Vaccines and Tuberculins in Prophylaxis and Treatment, 3rd edition. By H. J. PARISH. 227 pp., $5.00. Published for the Wellcome Foundation Ltd. by The Williams & Wilkins Co., Baltimore, Md.

Christopher's Minor Surgery. Edited by ALTON OCHSNER AND MICHAEL E. DEBAKEY. 547 pp., $9.00. W. B. Saunders Co., Philadelphia, Pa.

Current Therapy 1955. Edited by HOWARD F. CONN. 692 pp., $11.00. W. B. Saunders Co., Philadelphia, Pa.

Die Chirurgie der Peripheren Nerven. By HENRY NIGST, with foreword by Rudolf Nissen. 196 pp., Ganzleinen DM 29.70 ($7.10). Georg Thieme Verlag, Stuttgart, Germany. Also Intercontinental Medical Book Corp., New York, N. Y.

Doctors in the Sky. The Story of the Aero Medical Association. By ROBERT J. BENFORD. Foreword by John F. Fulton. 326 pp., $8.75. Charles C Thomas, Springfield, Illinois.

Fluoroscopy in Diagnostic Roentgenology. By OTTO DEUTSCHBERGER. 771 pp., $22.00. W. B. Saunders Co., Philadelphia, Pa.

Lehrbuch der Auskultation und Perkussion. By K. Holldack, with foreward by Curt Oehme, 195 pp., Ganzleinen DM 27. ($6.40). Georg Thieme Verlag, Stuttgart, Germany. Also Intercontinental Medical Book Corp., New York, N. Y.

Multiple Sclerosis. By DOUGLAS MCALPINE, NIGEL D. COMPSTON AND CHARLES E. LUNSDEN. 304 pp., $7.00. E. & S. Livingstone, London, England. Also The Williams & Wilkins Co., Baltimore, Md.

Pomp and Pestilence. Infectious Disease Its Origins and Conquest. By RONALD HARE. 224 pp., $5.75. Philosophical Library, New York, N. Y.

Potassium Metabolism in Health and Disease. By HOWARD HOLLEY AND WARNER W. CARLSON. 131 pp., $4.50. Grune & Stratton, New York, N. Y.

Progress in Nursing. A Survey of Recent Developments in Medicine and Surgery. Edited by ALAN MONCRIEFF AND KATHLEEN A. B. FOWLER. 269 pp., $4.50. Edward Arnold, Publishers, London, England. The Williams & Wilkins Co., Baltimore, Md.

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BENJAMIN FRANKLIN

Some Account of the Pennsylvania Hospital

PRINTED IN FACSIMILE WITH AN INTRODUCTION BY

I. BERNARD COHEN

Two hundred years ago, Benjamin Franklin published this account of the first permanent hospital in America. Anyone interested in the history of medicine will find a wealth of information contained in these pages written and printed by America's foremost citizen. In addition to the financial details of the Hospital's founding, Franklin includes an abstract of the first cases admitted, and their disposition.

The Introduction by I. Bernard Cohen puts the work into proper historical perspective and provides considerable new and detailed insights into the various influences which shaped Franklin's interest in public health.

$3.25

COTTON MATHER

First Significant Figure in American Medicine

BY

OTHO T. BEALL, JR. AND RICHARD H. SHRYOCK

The first aim of this study is to present the Reverend Cotton Mather in a new dimension—as "the first significant figure in American medicine." The authors show that the historic tendency to present Mather as merely a reactionary theologian gives far from the whole picture of the man. One of the most interesting features of the book is its reappraisal of Cotton Mather as one who, within the intellectual framework of his times and his profession, was a leading light of early American science.

Another objective of the authors has been to provide a detailed case study of medical thought in America at the beginning of the Eighteenth Century, a period hitherto largely overlooked as making any contribution to the field. Because this disregard has been the result of scarcity of materials, Mather is a particularly valuable source; he provides an almost unique mass of evidence concerning early American medicine, with all its implications for the social and cultural history of the times.

In the appendix will be found selected sections from Mather's chief medical work, "The Angel of Bethesda," here printed for the first time.

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(2) Therapeutic Nutrition, Publication No. 234, National Research Council.

Ask your Mead representative for your reprint of this recent clinical report on therapeutic nutrition and for detailed information on Sustagen . . . or write to Department C, Mead Johnson & Company.

Sustagen is easy to prepare and use

By tube . . . Sustagen® is given easily in hospital or home with Mead's Tube Feeding Set. The small, smooth plastic tubing is inserted and swallowed almost without sensation. Dilution: 1 cup Sustagen powder to 10 oz. water.

By mouth . . . Sustagen makes a good-tasting and satisfying therapeutic food-drink. Dilution: 1 cup Sustagen powder to 8 oz. water.

Therapeutic nutrition in therapeutic amounts

A 24-hour diet of 900 Gm. of Sustagen meets or exceeds the therapeutic nutritional recommendations of the Committee on Therapeutic Nutrition, National Research Council,[2] supplying:

Calories	3500
Protein	210 Gm.
Fat	30 Gm.
Carbohydrate	600 Gm.

. . . plus therapeutic amounts of 16 vitamins and minerals.

Sustagen is available through drugstores in 1 and 2½ lb. cans; to hospitals in 5 lb. cans also.

Mead's Tube Feeding Set is supplied individually packaged, ready for use.

MEAD JOHNSON & COMPANY
EVANSVILLE, INDIANA, U. S. A.

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